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BENIGN LESIONS OF THE CECUM SIMULATING CARCINOMA

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The differential diagnosis between benign and malignant lesions located in the cecal region of the gastrointestinal tract is not easily made. Of the 27 patients in this study, 11 had pathological lesions associated with the appendix. Eight of these had appendiceal abscesses, one a mucocele, and the other an inverted appendiceal stump. Cecal abnormalities were found in five patients during the course of examinations performed for the primary illness of regional enteritis. Lipomas, tuberculous lesions, and perityphlitis caused diagnostic confusion in nine patients. A hypertrophic mucosal fold and an actinomycotic infection were found in the two remaining patients. A definite diagnosis of the benign nature of these lesions was not possible except by direct observation. It is the opinion of the authors that when such doubt exists surgical exploration must always be done to establish the diagnosis and to provide appropriate treatment.

OCCASIONALLY a patient comes to operation with a preoperative diagnosis of carcinoma of the cecum that either has been made unequivocally or at least has been included as a distinct possibility, only to learn that the lesion is benign. We are presenting information on 27 such cases to demonstrate the various types of benign lesions that may be found and to emphasize some of the problems in differential diagnosis and management.

Several conditions have been reported as giving rise to such an error in diagnosis. The mistake has been due in part to the clinical impression of the disease based on some clue in the history or physical examination, or on the roentgenologic examination, but even at the time of operation some of these lesions have been thought to be malignant and have been treated as such, only to have the pathologist report a benign disease.

Congenital abnormalities, inflammatory lesions, benign tumors, defects of the ileocecal junction, and abnormalities either in the appendix or as a result of an inverted appendiceal stump have given rise to a number of these benign conditions.

It is most difficult, on the basis of physical and laboratory findings, to differentiate between a benign and a malignant lesion in the cecum. The

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symptoms in either disease may run the gamut from complete absence of symptoms to those of complete intestinal obstruction. As Puestow and Wheeler [1] stated, "The symptomatology and physical findings in diseases of the cecum are less diagnostic than of most other parts of the gastrointestinal tract."

As a rule, however, the patients we have subjected to abdominal exploration have had some definite symptoms which caused the examining physician to ask for roentgenologic studies and later for surgical consultation. The finding of a mass in the right lower quadrant has often caused the examiner to suspect a neoplasm, and rightly so; but it must be emphasized that not all such masses are malignant.

In establishing a diagnosis in the cecal region, the radiologist can often be helpful, but as Freedman and associates [2] pointed out, "In the cecal region, a variety of lesions and pseudolesions may simulate and must be differentiated from true polypoid adenomas. Among these are prominent ileocecal valve lips, resinous fecal clumps, submucous lipomas, and defects arising from adjacent inflammatory or neoplastic masses such as appendiceal or ileal granulomas, appendiceal mucoceles, carcinoids, carcinomas, etc."

Benign Lesions of the Cecum Simulating Carcinoma

Lesion	Cases, No.
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Without granuloma	4
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Inverted appendiceal stump	1
Actinomycosis of cecum	1
Hypertrophic mucosal fold	1
Total	27

*Due to perforation of appendix.

Probably the most troublesome problem of differentiation encountered by the radiologist is that of inverted stump of the vermiform appendix. Weber and Good [3] indicated that this stump may persist for some time as a bulbous mass projecting into the lumen of the cecum. Our experience is that this stump is not always silent, for it may bleed into the lumen of the intestine or cause intussusception.

The appendix can give rise to further confusion when it is not removed. W. J. Mayo [4] was the first surgeon to note that one cannot distinguish inflammatory disease about the vermiform appendix from true neoplasia. Likewise, there may be granulomas that form secondary to appendicitis and simulate neoplasms.[5] Wilson and associates [6] reported that these lesions are rare, occurring in approximately 1 per 75,000 patients admitted to the Mayo Clinic. They cited Bargen and Jacobs as suggesting that a sense of well-being, absence of anemia, and lack of the typical roentgenologic picture of carcinoma would help to distinguish granulomatous from malignant lesions. Most of these granulomas were a result of a perforated appendix, and most of these appendixes were situated in the ileocecal angle or in the retrocecal or retroileal regions, permitting the rapid sealing off of the appendiceal inflammation. These patients all had masses in the right lower quadrant of the abdomen. Le Brun [7] reported seven cases and noted the close clinical resemblance of periappendiceal granuloma to carcinoma.

In their series of unusual benign lesions of the cecum, Puestow and Wheeler [1] found congenital anomalies in 16 of the 30 patients whose cases were presented. Inflammatory lesions accounted for nine more cases, with three of these being due to amebiasis, two to tuberculosis, and one to talcum powder; the remaining three were nonspecific granulomas. Five tumors of the cecum were encountered: three carcinoids, one leiomyoma of the wall of the cecum, and one papilloma.

Cases Studied

Criteria.—The 27 patients of the present series were encountered at the Mayo Clinic in the period 1906 through June 30, 1959. We have included no patients who were found at operation to have had any type of abdominal malignant lesion or who had been known previously to have had a malignant lesion in the gastrointestinal tract. Carcinoids of the cecum have been considered as malignant lesions and thus patients with such lesions are not included. Patients with benign lesions of the cecum that were diagnosed clinically as such before operation (including a large number of patients suffering from regional enteritis) have been omitted. We have included patients regarding whom the clinician and radiologist were in disagreement over the diagnosis, but we have reported only on those who were found to have benign disease.

Observations.—Abscess formation occurring after perforation of the appendix was the leading cause of benign lesions of the cecum simulating carcinoma (see table). Of eight such lesions, four were associated with granuloma formation. All of these patients had a history of pain in the right lower quadrant. Three were operated on elsewhere and sent in with a diagnosis of probable carcinoma of the cecum made at the time of operation. Only two of the eight patients had noticed a mass in the abdomen, while seven had clinically palpable masses. One patient had noticed blood in his stool. In all of these patients, the history indicated that acute appendicitis had occurred at one time or another. In two, no roentgenologic examination was made. The radiologist thought that the underlying lesion was a tumor (probably carcinoma) in five cases and an extrinsic process in one case.

When granulomas are found in the cecal region and all other causes such as regional enteritis and tuberculosis are ruled out, the underlying cause is usually a previous perforation of the appendix. Musgrove and Dockerty[5] reported five cases of nonspecific periappendiceal granuloma in which careful search did not reveal an etiological factor: they concluded that perforation of the appendix appeared to have been the etiological basis for these granulomas. Often, the patient having such an abscess gives a history compatible with that of a ruptured appendix, and palpation of a mass in the right lower quadrant leads the clinician to make this diagnosis. It must be pointed out, however, that rupture of the cecum due to a perforating carcinoma can give a similar picture and must not be ruled out.

In view of the large number of cases of regional enteritis that we see each year, it is rather surprising that the erroneous diagnosis of carcinoma of the cecum has not been made more often in patients with this disease. Of the five patients we are reporting on, two were entirely asymptomatic but were found to have a mass in the right lower quadrant on physical examination. Two other patients had complained of pain in the right lower quadrant and their local physicians had found a suspicious lesion in the cecal region on roentgenologic examination of the colon. One patient came in with the signs and symptoms of partial intestinal obstruction. The radiologist thought that the lesion was unquestionably carcinoma in one of these five patients and probably extrinsic or inflammatory in the other four.

Lipomas may occur almost anywhere in the body and it is not surprising to find them in the gastrointestinal tract. In the cecal region, they often become pedunculated and may cause intussusception. They also ulcerate and have been incriminated as the cause of gastrointestinal bleeding. All five patients of our series had cramping pains in the right lower quadrant and some change in bowel habits, with diarrhea being the most frequent complaint. All five had intussuscepting lipomas. One patient had, in addition to the lipoma, a periappendiceal granuloma and abscess, lipomatosis of the ileocecal valve, a submucosal lipoma above the valve, and a sessile adenoma in the region of the valve. This patient is included only in the lipoma group in the table.

The radiologist is often able to give evidence for the diagnosis of benign cecal disease in the case of lipomas, because their fat content generally makes them more radiolucent than other masses arising in this location.[2] In the five cases of our series, the roentgenologic diagnosis was unequivocally that of carcinoma in two cases and that of possible carcinoma in the other three cases.

Tuberculosis of the abdominal cavity is not seen as frequently today as formerly. Older clinicians had a high index of suspicion, however, and they were accurate in making this diagnosis. These patients usually had evidence of pulmonary tuberculosis or other previously known systemic tuberculosis. The two patients represented in the table did not exhibit the usual picture of debilitating disease, nor was there any roentgenologic evidence of pulmonary disease. It is thus not surprising that the clinician and the radiologist came out positively for a diagnosis of carcinoma of the cecum. Tuberculosis is not completely eliminated today, and it should be included in any differential diagnosis when disease of the cecal region is suspected.

Two patients had no evidence of granuloma formation or of an abscess cavity, yet a mass of inflammatory tissue surrounded the appendix and led to the pathologist's diagnosis of perityphlitis. Both experienced pain in the right lower quadrant and were constipated. Roentgenologic examination, done in one of the cases, led to the diagnosis of probable carcinoma.

Most mucoceles of the appendix seen at the Mayo Clinic have been found incidentally at abdominal exploration for some other cause. One of the two patients in our series was referred to the clinic after exploration elsewhere because of a mass that had been found on routine physical examination and was thought to be a malignant lesion of the cecum. The lesion was otherwise asymptomatic. There was enough filling defect, however, to make the radiologist also consider the lesion probably malignant. The other patient was found to have a cecal lesion on roentgenologic examination of the colon during an investigation for intermittent diarrhea. The lesion was diagnosed as a possible carcinoma of the cecum, but was found to be a mucocele of the appendix at operation.

Comment

When this study was undertaken, it was thought that probably the most common cause of error in making a diagnosis of carcinoma of the cecum when a benign condition existed would prove to be the inverted stump of the appendix. This was not borne out, probably because of the careful attention that had been given to the clinical and roentgenologic findings. Actually, only one instance of an inverted appendiceal stump misdiagnosed as carcinoma was found in the series.

It has been observed at the Mayo Clinic that the inverted appendiceal stump may be demonstrated best roentgenographically by a modification of the double contrast method described by Weber and symptoms in either disease may run the gamut from complete absence of symptoms to those of complete intestinal obstruction. As Puestow and Wheeler[1] stated, "The symptomatology and physical findings in diseases of the cecum are less diagnostic than of most other parts of the gastrointestinal tract."

As a rule, however, the patients we have subjected to abdominal exploration have had some definite symptoms which caused the examining physician to ask for roentgenologic studies and later for surgical consultation. The finding of a mass in the right lower quadrant has often caused the examiner to suspect a neoplasm, and rightly so; but it must be emphasized that not all such masses are malignant.

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INTRACRANIAL LESIONS SIMULATING CEREBRAL THROMBOSIS

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Among a group of 303 patients having signs and symptoms of cerebral vascular disease 4 were later found to have pathological lesions of other than vascular origin. The histories of these four patients and two others, not of this group but exhibiting a similar situation, are here reviewed. The lesions discovered were subdural hematoma, cerebral abcess, two metastatic brain tumors, and two primary brain neoplasms. To limit errors of diagnosis and to obtain best results from therapeutic measures such as anticoagulation, the author advises that any patient with a stroke should have a complete and careful evaluation. When the medical history is inadequate, when atypical features are noted, or when the patient is younger than the age group in which cerebral thrombosis is usually encountered, both arteriography and pneumoencephalography should be seriously considered.

Renewed interest in the various clinical syndromes of cerebral thrombosis has accompanied the introduction of active therapeutic techniques. The availability of these measures makes an accurate and clearly etiological diagnosis all the more necessary.

In the course of studying a group of 303 patients with cerebral vascular disease, 4 patients with lesions simulating cerebral thrombosis were found. Another two similar cases were obtained from the files of the New York Hospital and are included because of their interesting features. These cases are presented as a warning that, even though a patient's medical history and clinical findings may be strongly suggestive of thrombosis, detailed investigation with lumbar puncture, electroencephalograms, arteriography, and pneumoencephalography may be necessary before commencing anticoagulant therapy.

Report of Cases

Case 1.—A 59-year-old man was admitted to the Second Neurology Division of Bellevue Hospital on Nov. 11, 1957. A complete medical history could not be obtained, because the patient was dysphasic and relatives were not available. He was able, however, to indicate that he had had a transitory episode of hemiparesis on the right side eight days prior to his admission and that one day prior to admission there was a sudden onset of right-sided hemiparesis with dysphasia which led to his hospitalization.

Results of examination were as follows: blood pressure 124/80 mm. Hg; receptive and expressive dysphasia; and grade 2 arteriosclerotic changes of the retinal vessels; hemiparesis, lower facial weakness, hyperreflexia, and bilateral extensor plantar reflexes were present on the right side. The left carotid artery pulsation in the neck was weaker than the right. Findings on roentgenographic examination of the skull were normal. The cerebral spinal fluid revealed clear, colorless fluid under normal pressure, and the protein value was 15 mg.%. The clinical impression was that of thrombosis in the left internal carotid-middle cerebral artery system.

On Nov. 29, 1957, as part of an angiographic study of strokes then being conducted by the Second Neurological Service,[1] a left carotid angiogram was performed. This did not demonstrate an occlusion, but an avascular area over the left hemisphere was apparent and, at operation, a subdural hematoma of about 60 cc. was evacuated. After this procedure the patient made a complete recovery and then remembered that he had been assaulted two weeks prior to hospitalization. He stated that at no time prior to the onset of his symptoms or after the attack had he experienced headache.

Comment.—In some of the patients described in this paper there are features in the medical history, physical examination, or laboratory findings which point toward a diagnosis other than cerebrovascular disease. However, this patient illustrates clearly some of the difficulties which may be encountered in the diagnosis of cerebral thrombosis. Even in retrospect it is difficult to see how, in the absence of an adequate history, the correct diagnosis could have been established without an angiogram. The limited available history and the course of the patient were suggestive of cerebral thrombosis. The onset was sudden, and the patient's course in the hospital was one of improvement in function and mentation. At no time was headache experienced, and the hemiparesis was accompanied by dysphasia. Dysphasia is an unusual feature in subdural hematoma.[2] The roentgenographic appearance of the skull and the cerebral spinal fluid were normal. This patient's correct diagnosis was established on-

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ly because routine arteriograms were then being performed as part of the cerebral vascular disease study.[1] It should be pointed out that loss of memory of a traumatic incident is not an uncommon occurrence in patients with subdural hematoma, and this frequently results in presentation of a misleading or inadequate medical history.

Case 2.—A 49-year-old man was admitted to the Second Neurological Service on Oct. 6, 1958. Three days prior to admission he had complained of a sore throat and the next day of a headache. On the day of admission he was found by his sister lying on the floor of his room at home.

Results of examination were as follows: The blood pressure was 170/100 mm. Hg. He had a receptive and expressive dysphasia and a moderately severe hemiparesis on the right side. The complete blood count was normal. The cerebral spinal fluid pressure was 150 mm. H_2O and a clear, colorless fluid with 5 lymphocytes per cubic millimeter and a protein level of 55 mg.% was obtained. Roentgenograms of the skull and chest were normal. The initial diagnosis was thrombosis in the left internal carotid-middle cerebral artery system. Two days after admission, a temperature of 101 F (38.3 C) was noted (the first temperature elevation recorded). He was treated with penicillin because of an inflamed throat (from which beta-hemolytic streptococci had been cultured), which was thought to be the basis of his fever. The next day his temperature was normal and did not rise again until the terminal events. On the third hospital day, an electroencephalogram showed a left-sided frontotemporal abnormality with a slow wave focus, and there were abundant spikes over the left cerebral hemisphere. From the 3rd to the 18th hospital days, his clinical course was that of improvement in the dysphasia and hemiparesis. He never complained of headache, and he looked well and was beginning to walk. Then, without warning, on the 18th hospital day he suddenly became unresponsive. There was no papilledema, nor was there evidence suggestive of a focal lesion in the nervous system. The cerebral spinal fluid pressure was 300 mm. H_2O with 1 lymphocyte per cubic millimeter and a protein level of 140 mg.%. One-half hour after lumbar puncture he developed focal fits on the right side, interspersed with generalized tonic seizures. A ventriculogram was immediately performed, and a shift of the ventricular system to the right was found. A craniotomy followed, and a large intracerebral abscess was discovered in the left frontal area anterior to the motor strip. Pus was also obtained from the left lateral ventricle. Culture from the abscess grew betahemolytic streptococci. The patient died a few hours later, without regaining consciousness. At autopsy an acute suppurative leptomeningitis was present, and a solitary large left frontal abscess was found.

Comment.—Certain features of this case take on added significance in retrospect. The patient's sore throat and headache prior to admission were given too little attention. However, the symptoms of hemiparesis and dysphasia were of sudden onset and during hospital observation improved appreciably over an 18-day period. Fever occurred but once, on the second hospital day, and was not impressive. The peripheral white blood cell count was normal. The entire course, until sudden worsening on the 18th day, was one of gradual improvement and therefore suggestive of the diagnosis of cerebral thrombosis. This case illustrates the insidious and confusing picture which may be presented by cerebral abscess.

Case 3.—A 61-year-old man underwent a cholecystectomy six weeks before admission to the Neurology Service. The day after operation he developed paralysis of the left side. In the ensuing period, until admission, little change occurred in the paralysis. On examination there was no papilledema. He had homonymous hemianopsia on the left side and a moderately severe left-sided hemiparesis, with slight sensory loss. The left plantar response was extensor.

Results of examination were as follows: Roentgenography of the chest and skull showed normal findings. The cerebral spinal fluid showed xanthochromia and a protein level of 106 mg.%, but no cells. Electroencephalograms showed slow wave activity on the right. The clinical diagnosis was cerebral thrombosis, but in view of the high protein level in the cerebral spinal fluid it was decided to undertake other studies to exclude a neoplasm or a hematoma. A right carotid arteriogram revealed no abnormality. On attempting a ventriculogram, a tumor cyst was probed in the right parietal region. Pathological examination of the cyst revealed it to be a metastatic undifferentiated carcinoma. Later the chest x-ray was reviewed, and a small erosion of the ninth rib was noted.

Comment.—The development of hemiparesis 24 hours postoperatively, as in this patient, is typical of the onset of some cases of cerebral thrombosis. In this case it was a purely coincidental development in the course of progress of the tumor. Unfortunately, the significant rib lesion in the chest x-ray had been overlooked initially.

Case 4.—A 58-year-old man suddenly developed difficulty in walking and a tendency to fall to the left, one week before admission. He had had symptoms of chronic pulmonary disease since 1948, and a diagnosis of bronchiectasis was made in 1954. In 1957 he developed the signs and symptoms of chronic pulmonary heart disease (cor pulmonale) due to bronchiectasis and obstructive emphysema. In the seven months prior to admission he had lost 50 lb. (22.7 kg.) in body weight.

Results of examination were as follows: blood pressure 150/90 mm. Hg, pulse rate 80 per minute. There was horizontal nystagmus, dysarthria, and marked cerebellar ataxia on the left and to a much lesser degree on the right side. Pain and temperature sensation was impaired over the left half of the body. The patient's gait was grossly ataxic. The cerebral spinal fluid was clear and colorless under normal pressure, with a protein value of 60 mg.%. Roentgenographic examination of the chest revealed a rounded nodule, 2 cm. in diameter, in the right peripheral lung field. The initial diagnosis was right superior cerebellar-artery thrombosis. The chest consultant thought that the pulmonary lesion was benign. In the first two weeks after admission the patient gradually improved, and his neurological signs decreased in severity. On the 14th day after admission he suddenly became much worse, with a decrease in alertness and an increase in the signs of cerebellar dysfunction. He improved again shortly thereafter, and on the 20th day he had few demonstrable neurological signs. On the 29th hospital day he became much less responsive, and findings that suggested brain stem disease were pronounced. Heparin was given intravenously to combat what was considered to be basilar artery occlusive disease. The patient died on the 30th hospital day.

Autopsy revealed a large tumor mass, with secondary hemorrhage, which involved a major portion of the brain stem, the vermis of the cerebellum, and the white matter and dentate nucleus of the left lobe of the cerebellum. Microscopic examination of the tumor indicated an anaplastic carcinoma. The primary tumor was in the lung.

Comment.—The signs and symptoms of basilar artery disease dominated the clinical picture seen in the fourth patient. In addition, the chest consultant believed the lesion in the chest to be benign. It therefore seemed reasonable to consider anticoagulant therapy in this patient when his neurological signs suddenly worsened, and it was postulated that thrombosis of the superior cerebellar artery had extended to the main basilar trunk. It should be noted that his course was characteristic of recurrent ischemic attacks of the basilar artery tree, with periods of remission of physical signs.

CASE 5.—A 54-year-old man had a generalized seizure one month prior to admission. Three weeks prior to admission he had complained of transient blurring of vision in the left eye lasting for two to three seconds, which occurred once more on the same day. On the day of admission he experienced further blurring of vision of the left eye, with retrobulbar pain and slight hemiparesis on the right side.

Results of examination were as follows. The blood pressure was 100/80 mm. Hg. Left-sided optic atrophy and slight right-sided pyramidal tract signs were present. No field defect was noted. The cerebral spinal fluid was clear and colorless at normal pressure, with a protein level of 42 mg.%.

The initial diagnosis was left carotid artery occlusive disease. A left carotid arteriogram was made and showed normal findings. Three months later the patient was seen with symptoms of decreased visual acuity in the left eye and an increase in the right-sided hemiparesis. The protein level of the cerebral spinal fluid was now 104 mg. percent. A pneumoencephalogram revealed a filling defect, and, at subsequent craniotomy a glioblastoma involving the optic chiasm and left optic tract was found.

Comment.—The fifth patient is most interesting to us because of the history of visual disturbances associated with motor weakness on physical examination. The association of these symptoms is thought to be a significant diagnostic feature of occlusive disease of the internal carotid artery.[3] In our series[4] we found this combination in 18% of such cases. Optic atrophy is a rare finding in carotid artery disease and would tend to influence physicians toward diagnosis of a tumor, as it did in this case. However, optic atrophy was found in 1 of the 57 cases of proved carotid artery occlusive disease described by us[4] and was described in association with this condition as far back as 1914 by Hunt.[5]

CASE 6.—A 56-year-old man, previously in good health, had brief attacks of loss of consciousness on two occasions, five and two days prior to admission. After the second attack he noted slight right-sided weakness. There was no complaint of headache. On admission to the hospital for investigation, minimal right-sided weakness was present. The carotid artery pulsation in the pharynx, though present, was weaker on the left side than on the right. Skull and chest roentgenograms were normal. The cerebral spinal fluid was at normal pressure, and the protein value was 58 mg.%. A clinical diagnosis of internal carotid artery occlusive disease was made, and a left carotid arteriogram was performed. The arteriogram, obtained after some technical difficulties (three attempts had to be made to puncture the artery), showed gross irregularity and narrowing of the internal carotid artery in the neck. A pneumoencephalogram showed slight symmetrical dilatation of the ventricles, without any filling defect or shift.

These studies were thought to confirm the clinical diagnosis, and anticoagulant therapy was started. During the next few weeks the right-sided hemiparesis progressed, and focal epileptic seizures occurred on the right side. The left carotid arteriogram was repeated six weeks later, and the carotid artery was seen to be normal in its extracranial portion but revealed pathological vessels in the left parietal area. At craniotomy, a large tumor (a glioblastoma multiforme) was found in the left parietal area.

Comment.—In the sixth patient the diagnosis of internal carotid artery disease was thought to be established at the first arteriogram, which showed poor filling and gross irregularity of the internal carotid artery. Seizures are known to occur not infrequently in patients with cerebral thrombosis (12.5% in one series).[6] Pneumoencephalography showed a symmetrically dilated ventricular system, without evidence of a local expanding lesion. This case illustrates the point that, on occasion, arteriography may falsely suggest arterial disease because of either spasm or trauma of the vessel wall during injection of dye. One should be alert to this possibility. In a recent arteriographic study on cerebral apoplexy, nonvascular lesions were present in 7 out of 100 patients, and it is likely that in any large series there will be a small group of patients in whom correct diagnosis will be other than cerebral vascular disease.[7]

On the other hand, cerebral thrombosis may give a clinical picture that is easily mistaken for that of a tumor. This is particularly true in patients with carotid artery disease, in whom headache and drowsiness with slowly progressive signs and even a shift of the ventricular system may be present.

Comment

Every patient entering a hospital with a stroke requires a complete and careful evaluation. When the medical history is inadequate, when atypical clinical features are noted, or when the patient is in a younger age group than that in which cerebral thrombosis usually is encountered, both arteriography and pneumoencephalography should be seriously considered. The risk of arteriography is well recognized. Nevertheless, the optimal use of active therapeutic measures, such as anticoagulant therapy, allows no room for error in diagnosis.

It is of interest that all but one of the patients described in this report were under 60 years of age, which is a decade younger than the age of peak occurrence of cerebral thrombosis.

Summary

Among six patients with intracranial lesions simulating cerebral thrombosis, whose cases are described, there was one with subdural hematoma, one with cerebral abscess, two with metastatic brain tumor, and two with primary brain tumor. Each patient illustrated a specific diagnostic difficulty.

Bellevue Hospital (Dr. Groch).

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EDEMA AFTER PROLONGED SITTING.—Varying degrees of edema can be detected after any mode of travel during which the passenger remains seated for a considerable time. In the sitting position, venous return from the feet is inhibited proportional to the distance of the vein below the level of the heart. A bending and kinking effect is imposed at the groin and knee regions. . . . Increased intra-abdominal pressure from sitting, wearing of a constricting belt or a garment, a large meal or abdominal distention due to decreased atmospheric pressure, compresses the inferior vena cava further impeding venous return. Immobility, compounded by drowsiness and sleep during flight, and inadequate leg room, intensifies the venous stasis of the sitting position by reducing the venous pumping effect of the leg muscles. Other factors which may have contributed to the thrombosis in this series are unrecognized venous disease, dehydration, occult alterations in coagulability and the trauma of the front edge and surface of the seat. . . . "Passenger phlebitis" should be suspected whenever calf pain or tenderness, lameness, painful walking, persistent or recurrent edema, chest pain or hemoptysis follow long flights. Passengers should be briefed regarding prolonged immobility in flight, particularly where previous venous disease or thrombosis has occurred.— Lieut. Col. M. J. Nareff, Passenger Phlebitis, *Aerospace Medicine*, November, 1959.

LIABILITY OF THE ANESTHESIOLOGIST AND THE SURGEON

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The medical anesthesiologist, unlike the nurse-anesthetist, exercises his professional duties concurrently with the surgeon. The relationship between surgeon and medical anesthesiologist is both ethical and legal. In most instances neither is liable for negligent acts of the other. The anesthesiologist is the master of his own techniques and must conduct himself according to the dictates of his own judgment. The anesthesiologist must give due consideration to the surgeon's requests for the care of the patient. The decisions here cited show that once the anesthesiologist enters into the performance of his contract with the mutual consent of the surgeon his legal duty is solely to the patient.

Traditionally, the surgeon has been granted authority to exercise control over all activities and personnel in the operating room. All persons associated with a surgical operation are under his direct supervision. Therefore, negligent acts performed by his surgical assistants, nurses, or other personnel, whether employed by him or not, are imputed to him by law in most states. He cannot directly or indirectly divest himself of this responsibility. These tenets have developed in common law out of legal and surgical necessity, for on some one person must rest the legal responsibility to the patient. This is stated in *Ruling Case Law* as follows.

> Probably the most common instance of malpractice which is brought into the courts arises out of surgical cases where the physician or attendant has left a sponge in the wound after the incision has been closed. That this is plainly negligence there is no doubt at all, and it matters not at all that many physicians testify that the best of surgeons sometimes leave a sponge or some other foreign substance in the bodies of their patients, for this is testimony merely to the effect that almost everyone is at times negligent. Whether the particular act was negligent is for the jury to decide, after considering the circumstances of the case. Surgeons cannot relieve themselves from liability for injury to a patient, caused by leaving a sponge in the wound after an operation, by the adoption of a rule requiring the attending nurse to count the sponges used and removed, and relying on such count as conclusive that all sponges have been accounted for (21 R. C. L. 388).

The Nurse-Anesthetist

The surgeon is responsible for the acts of the nurse-anesthetist. In law, she is a servant of the surgeon. Although the hospital employs the nurse-anesthetist and pays her salary, once she enters the operating room to administer an anesthesia she is under the sole direction of the surgeon. By the "borrowed-servant doctrine," agency causes this employee of the hospital to become the servant of the surgeon, under his exclusive control. Should her knowledge of the administration of anesthesia exceed that of the surgeon, she nevertheless remains his legal servant. Consequently, her errors are imputed directly to the surgeon. This doctrine is termed vicarious liability, and is usually applied when an agency, such as that of master and servant, exists. Neither she nor any other hospital employee in the operating room may accept or carry out any orders contradicting those of the surgeon. He is truly the "captain of the ship" (*Dohr* v. *Smith*, 104 So. 2d. 29 [1958]).

Status of the Anesthesiologist

With the advent of the medical anesthesiologist, the doctrine of total command of the operating theater is being challenged. Now, for the first time, another specialist—legally owing the same degree of care to the patient—exercises his professional duties concurrently with the surgeon. No longer is the surgeon in absolute control of the administration of anesthesia. Most surgeons welcome this sharing of responsibility, the professional assistance of a specialist in anesthesiology, and the improvement in the quality of anesthesia. However, some surgeons consider the new surgeon-anesthesiologist-patient relationship a denial of their authority and are hesitant to recognize the legal or ethical relationship between the anesthesiologist and the patient. This point of view is legally untenable.

In the last few years, the case law has defined clearly, on most points, the role of the anesthesiologist in the operating room. In analyzing the decisions of the courts, it must be remembered that surgeons and anesthesiologists are specialists; both are required to render care of a high quality to their patients. As one court stated, "Being employed because of their peculiar learning and skill in the specialty, it follows that their duty to the patient cannot be measured by average skill" (*Baker* v. *Hancock*, 29 Ind. App. 456, 63 N.E. 323, 64 N.E. 38).

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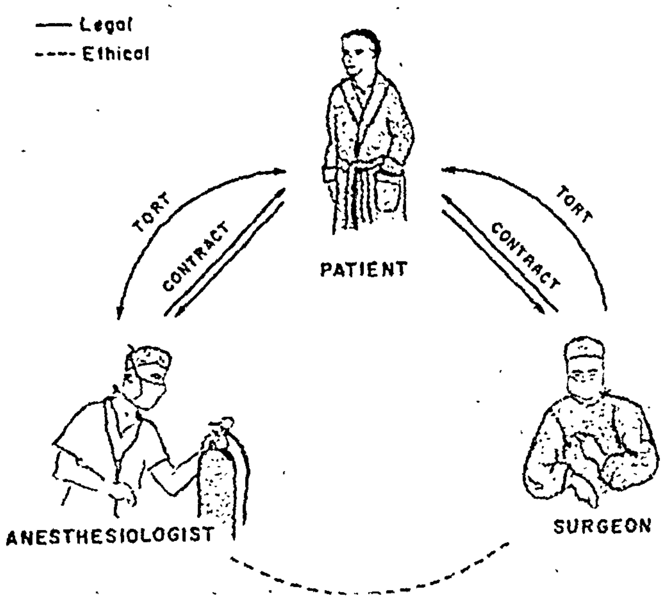
Read in the Symposium on Complications in Anesthesia before the Section on Anesthesiology at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 10, 1959.

Similarly, another court ruled, "They are bound to employ that degree of skill and knowledge which is ordinarily possessed by those who devote special study and attention to their particular specialty having due regard to the state of scientific knowledge at that time" (*Rann* v. *Twitchell,* 82 Vt. 79, 20 L. R. A. [N.S.] 1030, 71 Atl. 1045).

In a 1958 decision the court ruled, ". . . even assuming that . . . [surgeon] was 'surgeon-in-charge' or 'captain of the ship,' as urged, it does not follow that he is responsible for the negligence, if any, of an anesthesiologist such as Dr. X, assigned to the case by his own superior, exercising his own independent special medical knowledge in performing his duties without any specific directions from . . . [surgeon]" (*Thompson* v. *Lillehei,* 164 F. Supp. 716 [1958]). Decisions to the same effect, handed down between 1921 and 1956, were cited.



Cycle illustrating legal-ethical relationship between anesthesiologist, surgeon, and patient.

The presence of the medical anesthesiologist in the operating room does not create an agency between the surgeon and the anesthesiologist, nor is one the servant of the other. Each has his own contractual relationship to the patient (see figure). The duties of each evolve solely in contract. Although the surgeon is the prime contractor, his rights are neither prior nor superior to those of the anesthesiologist, once the operation has begun. The surgeon has a contract with the patient to perform a certain operation. The anesthesiologist, too, has a contract with the patient for the administration of anesthesia. The law imposes a collateral duty on each not to be negligent or, in other words, to exercise a certain degree of care in the performance of these contractual duties. But this duty is to the patient, and it in no way unites the anesthesiologist and the surgeon in a legal duty or status. This is not to say, however, that legal duties cannot be interposed. In most cases, the sharing of legal responsibility is left to the code of ethics of the medical profession. As such, it cannot be construed as a legal duty.

Negligence

The surgeon is not liable for the negligent acts of the anesthesiologist. Although the surgeon is said to be the captain of the ship, the court, in deciding the case of *Dohr* v. *Smith,* referred to the decision in *Hudson* v. *Weyland* (150 Fla. 538, 8 So. 2d. 37), which stated, in effect, that each is working in his own highly specialized field. In spite of their common goal, their responsibilities are not inextricably bound together. Even though the surgeon has secured the services of the anesthesiologist, the latter's contract is between himself and the patient. The mere recommendation of the anesthesiologist by the surgeon does not make him responsible for the anesthesiologist's malpractice (*Hitchcock* v. *Burgett,* 38 Mich. 501). An example of a court ruling follows.

> Surgeon's agreement with patient that she would not be given a spinal block meant that surgeon would do everything reasonably expected of controlling surgeon to see that she was not given one, but surgeon was not an insurer and did everything that he was obliged to do by making notation on hospital chart, which he intended anesthetist would read and which anesthetist did read, that patient was not to be given a spinal anesthetic, and there, surgeon was not liable for injuries allegedly resulting from spinal block.
>
> Anesthetist who was expert in administering the anesthetics was not surgeon's agent, when anesthetist administered anesthetic to patient.
>
> Controlling surgeon who chooses expert anesthetist and promises that spinal block will not be given does not thereby become insurer against administration of such anesthetic and will be an assaulter only if he fails to do what can reasonably be expected of him under the circumstances to prevent administration of such anesthetic (*Woodson* v. *Huey,* 261 P. 2d. 199).

Nor is the anesthesiologist responsible for the negligent acts of the surgeon. This point was determined clearly in a decision in which the court stated that "A physician who administers an anesthesia to a patient who is operated [on] by another is generally not liable for the negligence of the operating surgeon" (21 R. C. L. 394). In another decision the court said, "Since an anesthesiologist is directly chargeable with the physical condition of the patient in the operating room and his attention must always be directed solely to administering the anesthesia, he is not responsible for any carelessness of the surgeon performing the operation" (*Jett* v. *Linville,* 202 Ky. 198, 259 S. W. 43, 46 A. L. R. 1455).

However, there appears to be an exception to these general rules. In addition to each being answerable for his own conduct, each is answerable for all the wrongful and negligent acts of the other that he observes, or that in the exercise of reasonable care he should have observed, and that he lets go without objection (*Morey* v. *Thybo,* 42 L. R. A. [N.S.] 785, 118 C.C.A. 198, 199 Fed. 760, 46 A. L. R. 1455). Nevertheless, this obligation is limited. The one contractor need merely put the other on notice—that is, call his attention to the situation or negligent act. Once he has done so, his liability is relieved.

Differences of Opinion Between Anesthesiologist and Surgeon

Such, then, in brief, is the case law of liability of the anesthesiologist and the surgeon. Its application is extremely simple and clear. Nevertheless, some believe that the surgeon, as the prime contractor, has superior rights over the anesthesiologist. In all fairness, it must be remembered that the person being anesthetized usually is the surgeon's private patient. To him the surgeon owes moral, legal, and ethical duties. The patient looks to the surgeon for relief of his pathological condition. The surgeon must answer to the patient or to his family for mistakes or untoward happenings. Therefore, the anesthesiologist must give due consideration to the surgeon's requests for the care of the patient. This is an ethical—rather than a legal—duty.

However, difficult situations arise, especially in the choice of anesthesia. Not infrequently the surgeon requests the anesthesiologist to give anesthesia of a type that, in the judgment of the anesthesiologist, is contraindicated. In such a situation, the anesthesiologist must state his objection. Remembering his collateral duty of care to the patient, which the law imposes with his contract, he cannot compromise his own judgment, nor may it be commanded by the surgeon. Although an error in judgment alone is not sufficient to hold a physician liable for malpractice (41 Am. Jur. 198), his failure to act on the dictates of his judgment is. The following rule is an example. "The surgeon is charged with the duty of acting on his best bona fide judgment, and is not liable for injuries or death resulting without negligence, from honest errors of judgment, although it has been said that he is liable if his mistake of judgment is so gross as to constitute negligence. He may be liable also, if he fails to observe plain physical laws or physical facts which are governed by ordinary principles of intelligence and it has been held that, if a surgeon persists in the use of an anesthetic after a warning which would impel one of reasonable prudence to desist, he should be answerable for the consequences" (41 Am. Jur. 212).

The anesthesiologist, therefore, cannot discard his own judgment to satisfy the dogmatic and incorrect directions of the surgeon. If the surgeon remains adamant in his requests, and if the anesthesiologist cannot convince the surgeon of the proper anesthesiologic procedure, the anesthesiologist has but one action—to withdraw from the case. A cardinal rule in medical law is that a physician cannot be held liable for malpractice for not accepting a patient (*Hurley* v. *Eddingfield,* 156 Ind. 416, 59 N. E. 1058, 53 L. R. A. 135. *Randolph Adm.* v. *Snyder,* 139 Ky. 189, 129 S. W. 562).

However, for an anesthesiologist to begin a program that is, in his judgment, contraindicated, clearly furnishes grounds for a charge of malpractice. The simple expedient of recording the difference of opinion between surgeon and anesthesiologist in the patient's chart does not relieve him of liability if he chooses to give the anesthesia. In fact, such a record is an admission against interest and may be used in evidence against him. As one court stated, ". . . methods in a profession, however long continued, cannot avail to establish as safe in law that which is dangerous in fact" (*Ault* v. *Hall,* 119 Ohio 422, 164 N. E. 518). One professional person should never ask another to compromise his duties or judgment. If litigation should follow, the latter's acts of compromise are legally indefensible. The law leaves these differences of opinion for resolution according to the ethical principles of the professions of the persons involved.

Summary and Conclusions

Once the administration of anesthesia is begun, the theory of law that the surgeon is captain of the ship is in effect overruled, as it pertains to the anesthesiologist. The courts have consistently held that once the anesthesiologist enters into the performance of his contract with the mutual consent of the surgeon, his legal duty is solely to the patient. He is under no contractual duty or obligation to the surgeon. Each serves with the other by mutual consent, and each is entitled to make such division of authority as the circumstances may require (*Morey* v. *Thybo*). The anesthesiologist is the master of his own techniques. He must conduct himself according to the dictates of his own judgment. However, he has no license to proceed without regard for the anesthesiologic requirements of the surgeon. He is responsible for the exercise of reasonable care consistent with the requirements of the surgical procedure and his professional skill.

2020 E. 93d St. (6).

CONTINUING HAZARD OF AIR EMBOLISM DURING PRESSURE TRANSFUSIONS

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Fatal air embolism has occasionally resulted from pumping air into the transfusion bottle to hasten the passage of donor blood into recipient veins. Four case histories illustrate the type of situation, in operating or recovery rooms, in which the attention of those responsible for a transfusion was diverted long enough for air to enter the veins. Cardiac arrest occurred in each case. Resuscitative measures were successful only in one case. A patient with air embolism should be placed with head lowered and right side up. Rhythmic manual compression of the arrested heart can probably be carried out as well through a thoracotomy on the right as through a thoracotomy on the left. If speed in administering blood is considered essential, any transfusion apparatus can be modified so as to make it safe, and larger needles should be used.

Four occurrences of pulmonary air embolism with three deaths in our community within four years, while conventional pressure blood transfusion apparatus was being used, have alarmed us. Although a review of the American literature reveals only three reported deaths from this cause, personal communication with physicians and intravenous equipment manufacturers indicates that the actual incidence is probably much higher. The study of Dornette and Orth[1] shows that 1 in 108 deaths in the operating room was due to air embolism as a result of air being pumped into a bottle containing blood. Another fatality was reported in Louisiana.[2] Nicholson and Crehan[3] have reviewed the problem of air embolism and have listed as one of the causes the practice of pumping air into the bottle of blood.

The purpose of this review is to report four cases in which pulmonary air embolism occurred from pressure transfusions in which common air pressure methods were used without fool-proof safety devices and to point out the signs and symptoms of pulmonary air embolism, with a description of a modification of the method of treatment. We will describe the different types of apparatus that are presently available for safe, rapid blood administration and report on our investigation of plasma hemoglobin level changes with use of in-line transfusion apparatus. We shall also report on a new disposable apparatus under development which will allow pressure transfusions with safety. Figure 1 shows examples of the apparatus herein referred to as air-in-the-bottle or conventional pressure blood ansfusion apparatus.

While it seems safe to inject air or oxygen under ure into a bottle of blood to speed the rate of od flow, the possibility of producing air embolism exists even when the apparatus is carefully observed. The consequences of intravenous gas administration depend on several factors, the most important of which are the condition of the patient, the amount of gas injected, the rate of injection, the type of gas, and the bubble size. Elderly and debilitated patients are more susceptible to the harmful effects of air embolism than are young and healthy ones. Small amounts of air can be injected repeatedly into healthy persons with no apparent ill-effects. Cole[4] showed that oxygen, at a slow constant rate of not over 10 cc. per minute, can be injected safely into dogs over a long period, but that 20 cc. per minute is too large a volume and results in fatal gas embolism. Other workers[5] report similar results. This situation exists with respect to air also, but, because of its decreased solubility in blood as compared with oxygen, air is an even greater hazard.

Report of Cases

The following case reports illustrate the ease and rapidity with which fatal air embolism can occur during pressure blood transfusions.

Case 1.—A 24-year-old woman, admitted to the hospital in labor, was scheduled for an emergency cesarean section because she had had one previously. Preoperative anemia and moderately severe blood loss during operation necessitated rapid transfusion. This was accomplished by pumping air into the bottle with a blood pressure bulb. Immediately after delivery the anesthesiologist's attention was diverted elsewhere momentarily during the resuscitation of the newborn infant. When he checked the transfusion apparatus again, the bottle that had contained blood was empty and an undetermined amount of air had apparently entered the patient's

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vein. Thoracotomy was performed, and air was aspirated from the right ventricle. Cardiac massage was started, but the patient died despite treatment. An autopsy was performed and death was attributed to air embolism.

Case 2.—An 82-year-old woman with nonunion of a fracture of the right hip was scheduled for operation three days after admission. Preoperatively, her hematocrit value was 40% and her blood pressure was 130/80 mm. Hg. She was given meperidine, thiopental, nitrous oxide, cyclopropane and oxygen anesthesia. During the intramedullary nailing of the hip, her blood pressure fell to 80/50 mm. Hg and remained there during most of the time operation was being performed. During the administration of blood a steady flow was difficult to obtain so a blood pressure bulb was attached to the transfusion bottle and pressure applied. The patient remained in a state of shock due to the premedication, operation, anesthesia, and blood loss in spite of receiving 600 cc. of blood and phenylephrine rinses. After operation, the anesthetist returned the patient to the ward with the pump still in place. The ward nurse apparently was not aware of the pressure apparatus and the patient was left momentarily unattended. During that time the bottle emptied and apparently air embolism occurred. She was given vasopressors in an attempt to restore her failing blood pressure but received no other therapy. Permission to perform an autopsy was denied, but death was attributed to air embolism.

Case 3.—A 49-year-old woman was admitted with the preoperative diagnosis of fibrocystic disease of the left breast. Biopsy revealed malignancy, and radical mastectomy was performed during which she received thiopental, cyclopropane, and oxygen anesthesia. Since considerable blood replacement was needed, the third bottle was pumped in under air pressure. While the anesthetists were changing for lunch, the bottle emptied and an undetermined quantity of air entered the vein. The diagnosis of air embolism was made immediately, thoracotomy was performed, and cardiac massage was instituted, but with no success. Again, in this case, permission for an autopsy was not secured.

Case 4.—A 40-year-old man, who was an alcoholic, sustained several fractured ribs, a fractured left acetabulum, and head injuries as the result of a fall. Because of shock and what was thought to be marked blood loss, especially at the acetabular site, he received 12 units of blood. Two units were being administered at one time, and, to speed the rate of flow, both bottles were pumped full of air. The intern left the room momentarily; on his return he noted that one bottle had emptied and the air column extended to the patient. The patient had almost instantaneous cardiac arrest with resultant unconsciousness.

Because of the fractured left acetabulum, the patient was turned on his right side. The precordium was vigorously pounded and he was given 4 cc. of epinephrine in the myocardium. Positive-pressure oxygen was given using a Bennett machine. The heart began beating shortly after this therapy was instituted. Cardiac arrest, if it occurred, was thought to have lasted less than a total of three minutes. The patient recovered without any detectable residual.

Diagnosis

There are probably several reasons for the infrequent report of deaths due to air embolism. One of the reasons is that it is not always diagnosed as such, and death is sometimes attributed to other causes. This is especially true in institutions in which a minimum number of autopsies are performed or in which autopsies are conducted in such a manner that they would not reveal the presence of air embolism if it existed. Another reason is that it occurs infrequently in any one institution. And, finally, there is a natural reluctance to report such an avoidable death.

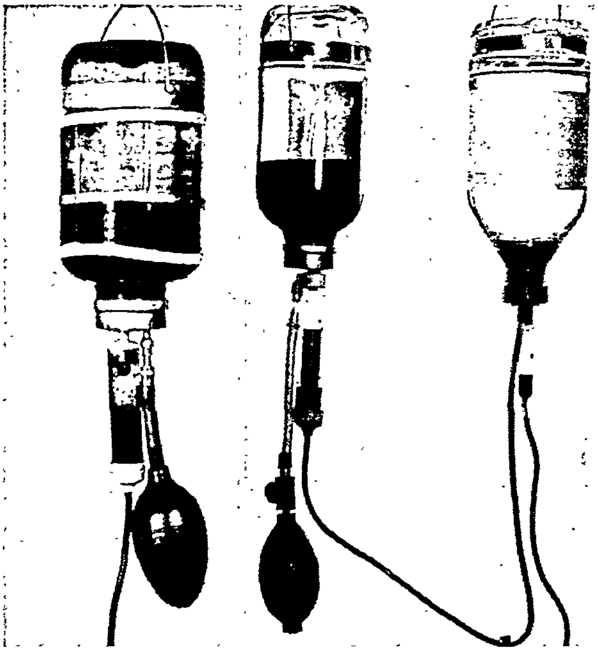

Fig. 1.—"Air-in-bottle" transfusion sets which may cause air embolism. *Right*, series arrangement is shown which provides safety trap but is not foolproof.

The clinical diagnosis of air embolism is usually made on the basis of the following signs: (*1*) a possible site of entry into the blood stream, e. g., an empty bottle that had contained blood which had been administered under pressure, with the column of air extending to the needle in the recipient; (*2*) sometimes, the sound made by the blood as it enters the vein, usually a high-pitched hissing noise;

(3) the presence of a loud churning sound audible to anyone in the room (termed the "mill-wheel murmur"); (4) increase in venous pressure with distention of veins; (5) fall in peripheral arterial blood pressure; (6) rapid, thready pulse; (7) cyanosis; (8) dyspnea; (9) cardiac arrest; and (10) syncope, due to cerebral anoxia if the patient is not already anesthetized. When these signs are present, especially the "mill-wheel murmur," the diagnosis of venous air embolism can readily be made. Once the diagnosis is made, treatment should be started immediately before permanent damage or death results.

In performing an autopsy in cases of suspected air embolism, certain precautions should be taken so that the presence of pulmonary air embolism will not be overlooked. In the usual technique the heart and great vessels are clamped off and opened as a unit, preferably under water. Any air is thus more easily demonstrated. Characteristically, the right heart and pulmonary artery will be found to contain a bright red froth which is the result of the thorough mixing of air and blood. Another important finding, if present, is a column of air bubbles extending from the site of injection to the right heart. This, however, is not always easy to demonstrate.

The original Virchow autopsy technique, in which nothing is disturbed until it has been thoroughly investigated and the organs are removed in a logical methodical manner, will be more likely to reveal this diagnosis. In this technique, as explained by Martland,[6] the abdomen and chest are carefully exposed. The sternoclavicular joints and the cartilage of the first two ribs are not disturbed for fear of cutting the vessels of the upper chest. The lower two-thirds of the sternum is removed without undue force. The pericardium is opened and the heart exposed. In the pulmonary type of air embolism, the right side of the heart is found to be distended, often ballooned out and tympanitic on percussion. The inferior and superior venae cavae are distended with what appears to be frothy blood. Then the pericardium, chest, and abdominal cavities are filled with water. The heart often shows a tendency to rise to the surface. If it is held back below the surface of the water as the right ventricle is incised, large bubbles of air and frothy foamy blood escape (in pulmonary air embolism). In any event, probably the most important factor in the correct postmortem diagnosis of pulmonary air embolism is that the pathologist be alert to the possibility of its having occurred.

Pathological Physiology

If only small amounts of air are injected, the air travels to the heart in the form of fine bubbles which are carried through the heart to the pulmonary arteries to be disseminated and absorbed in the lungs with no harmful effects. This sequence can be repeated numerous times in healthy animals. If, however, large amounts reach the heart rapidly, forming large collections in the pulmonary arteries, the air cannot be absorbed fast enough but remains as a froth to block the flow of blood from the right ventricle.[4] The air remaining in the right ventricle is compressed with each systole and is allowed to expand during diastole so that neither air nor blood flows. The resulting churning action accounts for the loud murmur described above.

Turning the patient so his left side is down and his head is lowered keeps much of the froth away from the pulmonic valve. The froth floats up into the region of the right atrioventricular valve, thereby allowing blood to flow again through the pulmonic valve. Gradually, small amounts of the froth are released from the right atrium and right ventricle and are distributed to the lungs where the air is absorbed. The occurrence of systemic air embolism is not possible unless there exists a patent foramen ovale, ductus arteriosus, or other anomaly allowing a right-to-left shunt of the blood.

Treatment

The therapy for a patient with venous air embolism is essentially the same, regardless of the source of the embolus, and consists of the following steps: (1) closure of the entry site, if possible, as by clamping off the transfusion tubing; (2) lowering of the head to prevent air from entering the cerebral circulation, which might occur if any air were able to reach the left side of the heart as through a patent foramen ovale; (3) placing of the patient in the left-lateral head down position (right side up) to promote accumulation of most of the air away from the pulmonic valve and thus allowing flow of blood rather than froth from the right heart; (4) if necessary, performance of an emergency thoracotomy, within two or three minutes after cardiac arrest or failure of the circulation, to facilitate cardiac massage and possible aspiration of air from the right ventricle or pulmonary artery with a needle and syringe; (needling the atrium may lead to serious bleeding); (5) maintenance of a patient airway and provision of artificial respiration with 100% oxygen; and (6) use of vasopressors to restore arterial blood pressure. Turning the patient to the lateral head down position (right side up), with use of vasopressors, may restore the circulation without necessitating cardiac massage or direct aspiration, providing cardiac arrest has not occurred.

Some question about therapy arises when air embolism occurs in a patient in whom severe hypotension is present and cardiac arrest is expected momentarily. Should the patient be turned right side up to promote collection of air in the right auricle, or left side up to facilitate cardiac massage?

This condition has been simulated in a series of experiments on three dogs in our laboratory. Pulmonary air embolism was produced by injecting air in 50 cc. increments into the femoral vein. The dogs tolerated the procedure while they were in the lateral (right side up) position, until 250 cc. of air in two minutes had been injected. When severe hypotension followed by cardiac arrest ensued, a right thoracotomy was performed. Froth was present in chest wall veins and the right heart was distended. Froth was allowed to escape through a 20-gauge needle from the heart (a larger needle leaves a hole which continues to leak blood). By opening the pericardium, cardiac massage could be accomplished almost as readily as through an incision in the left side of the chest. Blood pressure could be maintained at 50 mm. Hg during massage. Blood loss was considerable during the experiment. This, coupled with the large amount of air embolism, probably accounted for the lack of survival from this procedure.

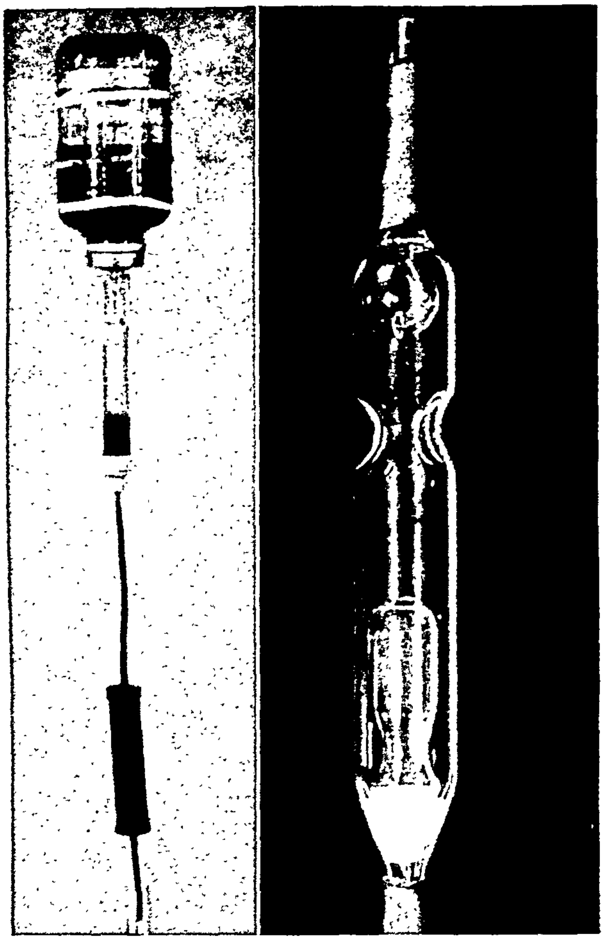

Fig. 2.—*Left,* in-line pressure transfusion pump. These are safe but require continuous manipulation to propel blood. *Right,* safety dropper. Float seats when blood has emptied from trap.

No clinical case of treatment of cardiac arrest, after pulmonary air embolism, by opening the right side of the chest (which position would promote better collection of air in the auricle and ventricle) for aspiration of the auricle, ventricle, and pulmonary artery and massage of the heart has been reported. From the animal experiments, we believe cardiac massage might well be successfully accomplished through a right-sided thoracotomy if the pericardium were opened. Further animal experiments and clinical reports will be necessary before this method can be established as generally advisable in cases of pulmonary air embolism.

Prevention of Air Embolism

At present there are several different types of apparatus commercially available for use in the rapid transfusion of blood with no danger of producing air embolism. All of them, to our way of thinking, have certain disadvantages that limit their use.

Commercially prepared in-line pumps have been available for three years (see fig. 2, *left*). The essential features of each of the in-line pumps are a flexible plastic bulb or chamber and one or a pair of one-way valves (either cork, plastic, or steel balls). The chamber is filled by gravity flow and is squeezed by hand, forcing the blood down the tubing to the recipient. Some models have a valve at each end of the pump, and some have only one valve at the top to prevent regurgitation into the bottle. The latter may allow aspiration of a small amount of blood from the patient's vein while the bulb is reexpanding after it has been squeezed. With use of one of these devices it is possible to administer a unit of blood in from three to five minutes (see table 1), no longer than with the old air-in-the-bottle technique. Compared with the old blood pressure bulb type of pump (in which air was placed in the transfusion bottle) one of the major disadvantages of this type of set is that it requires an extra person in the operating room to pump the blood. It is usually impossible for the

Table 1.—*Comparison of Flow Rates Obtained with Gravity, In-Line Pressure, and Plastic Bag Blood Administration Sets**

Set, Type	Material Pumped	Determinations, No.		Av. Time for 500 Cc., Min.	
		Gravity	Pumped	Gravity	Pumped
In-line pump A	Water	5	5	9.4	3.4
	ACD Blood	5	3	16.2	4.2
In-line pump B	Water	5	5	9.2	4.5
	ACD Blood	10	7	15.0	4.8
In-line pump C	Water	5	5	9.8	3.9
	ACD Blood	5	3	15.9	4.9
In-line pump M	Water	5	5	10.1	3.9
	ACD Blood	5	4	16.6	4.9
Plastic Bag					
Gravity only	Water	5	...	14.2	...
With pressure jacket	Water	...	5	...	4.0
Hand squeezed ...	Water	...	5	...	3.7

* All determinations made with 18-gauge needles at outlet and 40-in. columns of fluid.

anesthesiologist to neglect some of his other duties to assume the task of pumping blood for the patient. If no other person is available to assume this responsibility, this will definitely handicap the anesthesiologist who wants to speed up a slow blood transfusion.

Table 2.—*Plasma Hemoglobin Levels Before and After Passage Through In-line Transfusion Pumps*

Type	Case, No.	Hemoglobin Levels Bottle Mg./100 Cc.	Tubing, Mg./100 Cc.	Difference, Mg./100 Cc.	Increase %
A	1	32.7	30.6	−2.1	
	2	13.3	13.0	−0.3	
	3	23.0	23.0	0.0	
B (Cork float type single chamber) ..	4	68.2	178.0	109.8	161.0
	5	98.0	113.0	15.0	15.3
	6	23.0	32.5	9.5	41.3
	7	19.3	44.5	25.2	131.0
	8	11.3	44.5	33.2	291.0
	9	59.6	77.6	18.0	30.2
	10	42.6	51.0	8.4	19.7
C (Single chamber)	11	35.0	106.0	71.0	203.0
	12	18.8	36.8	18.0	95.7
	13	53.1	65.0	11.9	22.4
M	14	59.7	19.7	−40.0*	
	15	42.5	38.0	−4.5*	
	16	22.4	60.4	18.0	214.0
	17	33.0	40.0	7.0	21.2
Total		685.5	1063.6	328.1	
Mean		40.3	59.0	18.71†	

* Reversal due to insufficient time of tubing samples in centrifuging.
† Significant at 0.05 level.

Another possible drawback to the use of the in-line pump is the amount of hemolysis produced by the squeezing and regurgitation of the red cells. In table 2 are summarized the results of plasma hemoglobin determinations on stored citrated blood before and after it was pumped with four types of commercial in-line blood pumps. In this study a blood sample was withdrawn from the transfusion bottle prior to transfusion with an in-line pump; then a similar sample was drawn as the last 100 cc. of blood was being pumped into the patient. The second sample was taken from the intravenous tubing near its entry to the needle in the patient's vein. Both samples were centrifuged and the plasma refrigerated until plasma hemoglobin determinations were performed. The benzidine base and hydrogen peroxide analytical method of Crosby and Furth[7] was used. The results are tabulated in table 2. The wide variation in hemoglobin levels is generally a reflection of prior hemolysis in the stored citrated blood. Plasma hemoglobin levels increased 18.8 mg. per 100 cc. This amount of hemolysis probably is not significant[7A] unless large amounts of blood are administered and renal function is impaired.

Hale[8] and Foreman[9] report the use of in-line traps to be used with rapid arterial and venous blood administration (see fig. 2, *right*). This type of apparatus consists of a glass chamber containing a glass float inside. The bottom of the chamber and of the float are of ground glass and are made to match and form a tight fit. As the last of the blood drains from the chamber, the float descends, seating itself in the bottom and forming a closed valve which allows no air to follow down the tube to the patient. Although these sets have been used 1,600 times at the Cleveland Clinic, no cases of air embolism have been observed. The disadvantages of this type of safety device are as follows: (1) the initial cost makes it necessary to clean, resterilize, and reinsert it in special tubing after each transfusion rather than discarding it after use; (2) it is breakable; and (3) it must be handmade and therefore is not generally available.

The use of plastic bags for storage and administration of blood is a relatively recent addition. This method of transfusion has certain advantages over the use of conventional bottles, but there are also certain drawbacks associated with it. The plastic bag (see fig. 3) may be squeezed by hand or placed in a pressure jacket to speed the flow of blood. With the use of the pressure jacket, it is possible to pump 500 cc. of blood within two to five minutes (see table 1) at a steady and even flow. No special attention is necessary to watch this type of apparatus and it is completely safe. Other advantages are as follows: (1) convenience in storing and shipping empty bags; (2) minimal loss of platelets; (3) ease of disposing of used bags; and (4) little breakage.

The following disadvantages are associated with the plastic bags: (1) Blood bank personnel report difficulty in drawing blood from the donor (the bags fill slowly, a large needle is needed, and the tubing may become plugged with clotted blood); (2) at the present time blood bags are slightly more expensive than glass bottles; and (3) they are not standard items in commercial and Red Cross blood banks.

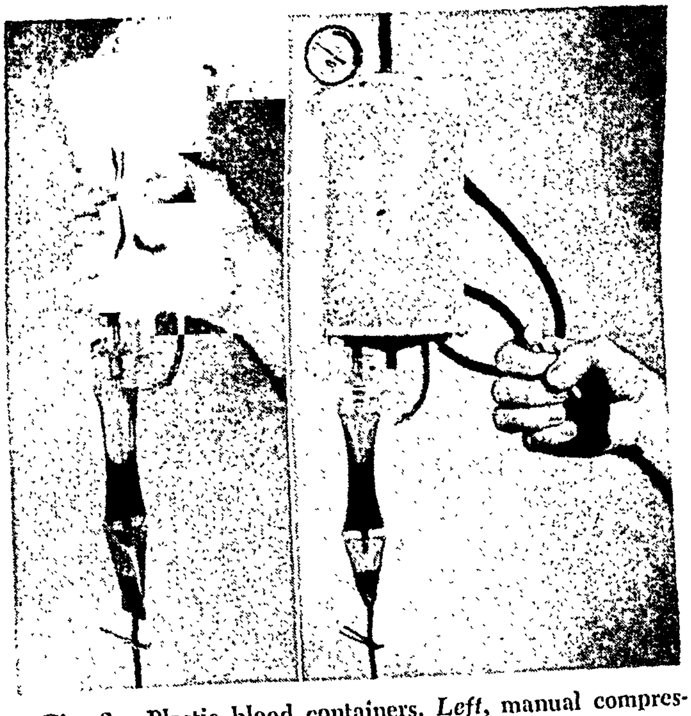

Fig. 3.—Plastic blood containers. *Left*, manual compression of bag. *Right*, pressure cuff is shown, which speeds transfusion without continuous pumping.

With the series hookup (fig. 1, *right*) the blood flows through a bottle of saline solution before reaching the patient. When the blood bottle empties, the air flows into the saline solution, making it necessary for that bottle to be empty also before the air can flow to the patient. The disadvantages of this type of apparatus are as follows: (1) it lessens but does not eliminate the danger of air embolism and must be watched closely; (2) it is more bother to assemble than a single unit; (3) unnecessary fluid may be administered or some blood will be discarded; and (4) it cannot be used with some types of fluid administering apparatus.

With the use of the syringe and three-way stopcock, blood can be pumped in rapidly enough. However, this requires the use of a second person, is cumbersome, probably is not altogether sterile, and may well produce more damage to the red blood cells than any of the other methods. The use of a recently developed plastic three-way stopcock, together with plastic syringes, is a marked improvement over the conventional three-way stopcock and glass syringe. The rotating eccentric wheel pump is no longer available commercially. This was a hand-operated pump which in effect stripped the tubing forcing the blood into the patient.

Description of a New Apparatus

Since none of the above described pieces of apparatus combined both convenience and safety, we were anxious to devise a more satisfactory piece of apparatus for pressure transfusions. One has been devised which is still in experimental development (see fig. 4). This device is constructed of plastic and is designed to be disposable. The basic mechanism is a chamber containing a ball float. When blood is flowing the chamber fills and the ball rises to occlude the upper outlet (termed the air escape valve). When in this position, blood flows out the lower outlet and through a tube to the patient. As the bottle empties, the blood level falls in the chamber and the ball float also falls. This opens the upper outlet and allows any remaining pressure in the bottle to escape. The float then descends with the blood level to the bottom of the chamber where it closes that outlet, thus providing a secondary safety factor, preventing air from reaching the patient. Preliminary work with this apparatus is underway, but so far it cannot be made to "fail safe." It is not yet in commercial production.

Comment

The occurrence of three deaths from pressure transfusion in this city during or after administration of anesthesia, over a period of two years when about 45,000 anesthesias were administered, gives a mortality of 1:15,000. Only three other deaths from this cause can be found in a review of the literature. However, personal conversations with physicians across the country suggest that the true incidence of this complication elsewhere is not unlike the incidence here. When one considers that the death rate connected with anesthesia from all anesthetic causes has been reported as low as 1:9,000 [10] then the hazards of air embolism from mishandled pumps appear significant.

The only hazard from abandoning the use of air pressure transfusion apparatus would seem to come from failure to deliver blood rapidly enough. During the past three years, when an in-line transfusion apparatus has been used in about 98% of cases when blood might have to be speeded in this hospital, no fatalities ascribable to too slow blood transfusion (which could have been prevented by the more convenient but hazardous air-in-the-bottle technique) have been reported to us. When a large needle (15-gauge or larger), plastic tubing such as the Rochester needle [11] or Intracath [12] or multiple needles are used, blood can be given as rapidly as needed or the patient can withstand it (without producing serious hypothermia or citrate intoxication) by the in-line pump method.

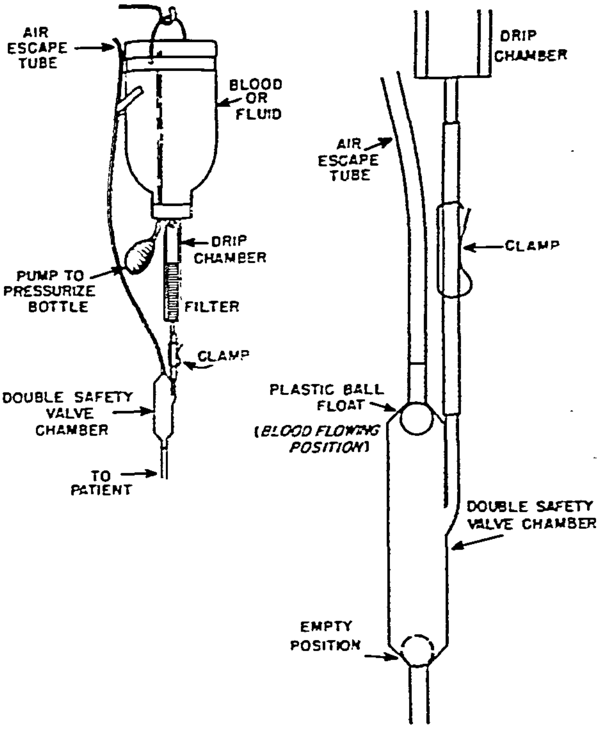

Fig. 4.—Safety trap under development. Floating ball valve serves dual purpose. In high position it allows blood to be forced to patient under pressure, and in bottom position it prevents air from reaching patient while allowing it to escape through outlet.

If all physicians would demand that their hospital blood banks and local Red Cross blood banks furnish blood in plastic containers, a yet more convenient method of rapidly transfusing blood would become generally available. The drawback here is that probably most blood users are not giving the blood rapidly and and hence are not asking for the change. Walters and co-workers[13] and Strumia and colleagues[14] stated that blood preserved in plastic bags shows less loss of platelets and longer red blood cell life than blood drawn in siliconized tubing and stored in siliconized bottles. Less preservative is needed when bags are used instead of bottles. All of these arguments make the case for plastic containers for blood a strong one. Apparently, the only factors holding back the widespread use of plastic blood bags are the economic factor, a general lack of appreciation of the hazards attendant on the use of blood bottles and pressure transfusion apparatus, lack of knowledge of the advantages of plastic bags over glass bottles, and a passive acceptance of in-line blood pumps as a safe but cumbersome substitute to "air in the bottle" method of speeding transfusions.

Since the use of plastic bags appears to be the safest and most feasible rapid transfusion method, it behooves all physicians in the United States to request that our blood banks institute their universal use. As the sale of blood bags would be increased, certainly the cost of these bags would drop to the point in which blood banks would suffer no economic loss from this change to plastic containers, and, most important, lives would be saved. If the military and civil defense authorities would lend their support to this method, certainly the change would be facilitated, but until blood banks uniformly furnish blood in plastic bags, physicians will need other means of speeding transfusions. The American Red Cross network of blood banks is at present contemplating the change to plastic bags, although no definite date for this has been set.[15] In the meantime, hospitals and physicians need to become aware of the hazards of air embolism from the use of air under pressure transfusion apparatus. In-line pumps need to be made universally available. Which in-line pump is better depends on individual preferences and needs. But forethought is necessary since changeover to an in-line pump from ordinary transfusion apparatus is cumbersome when rapid transfusion is suddenly needed.

Summary

Four cases of pulmonary air embolism (with three deaths) during the use of "air-in-the-bottle" type of pressure transfusion have alerted us to the need for safer pressure transfusion methods. Pulmonary air embolism, when it occurs for any reason, should be treated by placing the patient with his head lowered and his right side up, to allow the air to be trapped in the right auricle and away from his pulmonic valve. If cardiac arrest occurs, it should be treated by thoracotomy, air aspiration, and cardiac massage. While the use of the safety dropper, syringe and three-way stopcock, the rotary pump, or the in-line pump is usually adequate, we find the blood bag more satisfactory for the rapid administration of blood. Use of the in-line blood pump increased the plasma hemoglobin level from an average of 40.3 mg. per 100 cc. of blood to 59 mg. per 100 cc. of blood, probably not a serious hazard when only a few transfusions are given. Foresight, careful technique, and eternal vigilance will prevent the occurrence of iatrogenic pulmonary air embolism, an all too frequent catastrophe.

2033 S. State St. (15) (Dr. Ballinger).

The Safety Dropper used in this study is not commercially available. Requests for further details should be addressed to Dr. Donald Hale, Cleveland Clinic, Cleveland, Ohio.

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LONG-TERM FOLLOW-UP OF PATIENTS WHO RECEIVED 10,098 SPINAL ANESTHETICS

IV. NEUROLOGICAL DISEASE INCIDENT TO TRAUMATIC LUMBAR PUNCTURE DURING SPINAL ANESTHESIA

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and
Robert D. Dripps, M.D., Philadelphia

A critical evaluation of spinal anesthesia was made by studying the records of 8,460 patients who received 10,098 injections of spinal anesthetics; this group was compared with a group of 1,000 persons who received general anesthetics for the same types of operations and with 100 persons who received spinal anesthetics after induction with general anesthetics. No instance of adhesive arachnitis, transverse myelitis, or cauda equina syndrome was found, but neurological complications occasionally resulted from lumbar puncture per se. Two cases are described in which various persistent symptoms and disabilities followed unsuccessful attempts at administration of spinal anesthetics; in 17 other cases of difficult lumbar puncture paresthesias and other complaints occurred after the successful injection of the anesthetic. In spinal anesthesia proper selection of patients is essential, and lumbar puncture, whether for purposes of diagnosis or anesthesia, must be performed with meticulous attention to certain well-known details of technique.

Spinal anesthesia is, in our opinion, one of the safest and most satisfactory of all anesthetic techniques when properly understood and managed. It is unfortunate that its good and bad points have not been more realistically appraised by members of the medical profession. Many neurologists and neurosurgeons fear the method because they believe that neurological sequelae are inevitable. Many anesthesiologists have abandoned the technique because of the possibility of lawsuits when postanesthetic complications develop. Yet carefully observed series have demonstrated that major neurological consequences need not occur and that minor neurological sequelae can be minimal with reasonable care.[1] An analysis of so-called anesthetic deaths showed that relatively few occur in patients under spinal anesthesia.[2] A paradox is therefore evident. Unsubstantiated clinical impressions have overruled careful observations, and patients are being denied the benefits of a valuable anesthetic technique.

Since we believed that spinal anesthesia was the method of choice for certain operations and offered additional advantages in others, we made a decision 11 years ago to study spinal anesthesia as objectively as possible. It was evident that the most serious objections to the technique were the fear of hypotension occurring immediately after the subarachnoid injection of a local anesthetic and the fear of delayed complications involving the nervous system. The latter group of sequelae were regarded as unpreventable by many. Foster Kennedy in 1950 had stated that "from a neurological point of view we give the opinion that spinal anesthesia should be rigidly reserved for those patients unable to accept a local or general anesthetic. Paralysis below the waist is too large a price for a patient to pay in order that the surgeon should have a fine relaxed field of operation."[3]

During the period 1948 to 1951 every person who was given spinal anesthesia at the Hospital of the University of Pennsylvania was studied according to a prearranged plan. A total of 8,460 patients given 10,098 injections of spinal anesthetics was available for study. The incidents associated with lumbar puncture, the local anesthetic used, and the immediate and postoperative effects were consistently and carefully recorded. During the hospital stay the patients were seen almost daily by the anesthetist or by a trained nurse. Questions were asked that could lead to the early discovery of the types of neurological disease alleged to result from spinal anesthesia. Before leaving the hospital all patients were requested to reply to a questionnaire that would be mailed to them within six months. The advantage of the immediate phase of this study was that all of the facts about the technique of administration of spinal anesthetics, the details of the operation, and the immediate postoperative effects could be gathered in significant numbers in one institution where the habits of the anesthetists were known. This search for complications in all probability invited extraneous com-

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Read in the Symposium on Complications in Anesthesia before the Section on Anesthesiology at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 10, 1959.

plaints from the patients, but only this method could uncover the neurological disease which ordinarily might have passed undetected.

A parallel study was conducted in a group of 1,000 persons who were placed under general anesthesia for the same types of operations as those in which the first group were put under spinal anesthesia in order to uncover those symptoms and signs that might be common to the type of patient or to the operation performed. A smaller series of 100 patients were placed under spinal anesthesia only after the induction of general anesthesia to rule out or assess those symptoms and signs that could arise purely on a psychic basis.

Accurate information was obtained for 89% of the total number of injections of anesthetics for periods which now range from a minimum of six months to a maximum of 10 years. No instance of adhesive arachnitis, transverse myelitis, or the cauda equina syndrome was found.[1a] As with all anesthetic techniques, minor problems were discovered. Minor neurological deficits were noted, but none were progressive or of any consequence.[1b] In this study 11 patients were found who showed exacerbation of neurological disease after spinal anesthesia.[4] Although a cause-effect relation could not be proved, we believe that spinal anesthetics should not be given to a patient with disease of the nervous system. This admonition applies to persons with congenital, acquired, inactive, or active disease. The restriction includes trauma, bacterial and viral infections, degenerative diseases, neoplasms, and systemic diseases with neurological accompaniments.

It became apparent that neurological complications of spinal anesthesia can result from lumbar puncture per se. Several causal factors may be involved. Best known are those complications attributable to leakage of cerebrospinal fluid, which gives rise to the syndrome of decreased intracranial pressure, comprising headache and ocular and aural symptoms.[5] These can be minimized by use of a small gauge needle.

We now present a group of cases in which trauma produced by the lumbar puncture needle appeared to produce neurological signs and symptoms. Backache and infection have been reported [6] as a sequel of lumbar puncture, but neurological deficit resulting from trauma has not been emphasized. The aim of this paper, therefore, is to record our findings and to plead again for the careful performance of lumbar puncture whether for diagnostic reasons or as a part of spinal anesthesia.

Report of Cases

CASE 1.—A 23-year-old man was to have a fistula in ano excised. He had had no previous anesthesia or history of systemic disease. He had occasional headache and backache, but none were severe. Spinal anesthesia was selected although the skin of the back was scarred and marked with keloid as a result of burns suffered in childhood. Many attempts at lumbar puncture with a 22-gauge needle were made in two interspaces with the patient in the sitting position. Severe paresthesias were experienced in both legs. Although the subarachnoid space was entered and clear cerebrospinal fluid obtained, spinal anesthesia was abandoned because paresthesias were noted every time attempts were made to withdraw fluid. Proctoscopy and excision of the fistula were then carried out during anesthesia induced by thiopental sodium, decamethonium bromide, and nitrous oxide.

On the first postoperative day, as soon as he arose from bed, this man had severe headache beginning in the back of the neck and radiating around the side of the face to the eyes. He also noticed tenderness and pain at the site of lumbar puncture reaching to the lower back. There was no numbness or difficulty in voiding or walking. A week later when he returned to the hospital postural headache and severe back pain were still present. He walked with the aid of a cane in the semistooped position. Pain in the left calf was now present, but there was no subjective paresthesia or numbness. After urination there was a sensation as if the bladder were incompletely emptied, and he had experienced considerable diminution in sexual drive. Neurological examination showed negative results except for tenderness over the spines of the third, fourth, and fifth lumbar vertebrae. Subsequently the patient's condition improved, and he resumed work as a machinist. However, eight months after operation after an exacerbation of back and leg pain the findings were suggestive of protruded disk either at $L_{3\text{-}4}$ or $L_{4\text{-}5}$. He was treated conservatively.

Comment.—There can be little doubt about the relation between the development of back and leg pain and traumatic puncture. Since a local anesthetic was not injected into the subarachnoid space, intraneural or intraspinal injections obviously were not made. Likewise we believe that the patient's complaints were genuine although they were associated with considerable emotional stress.

The decision to abandon spinal anesthesia in this case was the correct one although it should have been made sooner. The deciding factor was inability to eliminate paresthesias with any position of the needle. Under such circumstances injection of the local anesthetic was unthinkable.

CASE 2.—A 32-year-old woman was scheduled to receive spinal anesthesia for cesarian section. She had been given spinal anesthesia four years before the cesarian section without complication. On this occasion, with the patient in the lateral decubitus position, numerous attempts at lumbar puncture with a 22-gauge needle were made in the fourth, third, and second interspaces, but they produced many paresthesias in both legs, thighs, and feet, more severe on the left. At one time blood-tinged cerebrospinal fluid was recovered. Ultimately subarachnoid tap produced a scant quantity of clear cerebrospinal fluid. A total volume of 1.6 ml. of local anesthetic containing 8 mg. of a 1% tetracaine hydrochloride solution and 0.8 ml. of a 10% dextrose solution was injected without additional paresthesias, but anesthesia was unsatisfactory. Supplementary general anesthesia induced with nitrous oxide and thiopental sodium was required.

In the postoperative period this intelligent woman stated that sensation returned more slowly to the left leg than to the right. Early complaints were backache at the puncture sites and a feeling of weakness in the left leg. She was at first unable to lift the left leg because of motor weakness and loss of position sense. On standing she tended to lose balance and bore most of her weight on the right leg. She also complained of spasmodic pain on voiding. Symptoms gradually abated, and on the eighth postoperative day residual neurological signs were minimal hypalgesia over the anterior left thigh and a slight motor weakness in the entire limb, but she had normal reflexes. No other sensory defect was found.

Methods and Results of Lumbar Puncture in Seventeen Patients

Patients								
Case No.	Age, Yr.	Sex	Operation Performed	Anesthetic Injected	Attempts, No.	Site of Paresthesia	Complaint	Duration of Side-effects
1	24	M	For coccygeal sinus	Tetracaine dextrose	3	Rt. leg	Shooting pains rt. leg	1 da.
2*	28	F	For coccygeal sinus	Tetracaine dextrose epinephrine	1	Lt. leg	Shooting pain and numbness lt. leg	2 da.
3	34	M	Appendectomy	Procaine and epinephrine	1	Lt. buttock, penis	Paresthesia lt. buttock and penis	2 da.
4	43	F	Hemorrhoidectomy	Tetracaine dextrose	4	Lt. thigh, buttock	Pain lt. thigh to knee	1 da.
5	47	F	Hysterectomy	Tetracaine dextrose epinephrine	2	Rt. buttock, groin	Weakness rt. leg, pain rt. leg	8 da.
6	29	F	Cesarean section	Tetracaine dextrose	2	Rt. leg	Rt. leg paralyzed, pain	2 wk.
7†	36	M	Appendectomy	Tetracaine dextrose	2	Rt. thigh	Numbness and tingling in rt. thigh	3 wk.
8†	41	M	For varicose veins	Tetracaine dextrose	1	Rt. leg	Numb area rt. foot	2 wk.
9	54	F	Cholecystectomy	Tetracaine dextrose	1	Lt. leg	Sharp pains lt. leg	Few wk.
10	30	F	Exploratory laparotomy	Tetracaine dextrose	2	Rt. leg, rt. shoulder	Pain rt. shoulder and rt. thigh, numbness rt. thigh, paresthesias	1 mo.
11	31	F	Vaginal plastic	Tetracaine dextrose epinephrine	4	None	Pain lt. calf and lt. foot, numbness	1 mo.
12	35	F	Hysterectomy	Dibucaine hydrochloride	1	Lt. leg	Pain lt. leg	Months
13	38	M	Appendectomy	Tetracaine dextrose	Many	Rt. toes, both heels	Burning pain in heels	Months
14	29	F	Delivery	Tetracaine dextrose	2	Rt. leg	Numbness rt. thigh	6 mo.
15	39	M	Incision and drainage, rectal abscess	Procaine cerebrospinal fluid	2	Lt. leg	Pain lt. leg	1 yr., intermittent
16	40	M	Cholecystectomy	Tetracaine procaine	5	Rt. leg	Shooting pain rt. foot	6 mo.
17	65	M	Cholecystectomy	Procaine epinephrine	1	Lt. leg	Pain lt. leg	Intermittent

* Cerebrospinal fluid was bloody in this patient only.
† A 22-gauge needle was used in all but these patients, in whom a 20-gauge needle was used.

Three months after operation she showed marked improvement but complained of occasional loss of balance, a sensation as though the third and fourth toes were flexed, and several episodes of involuntary defecation. Neurological examination showed negative results. After five years of observation the only residual complaints were sensations of pain and numbness in the heels and toes when she was tired.

Comment.—This patient had successfully undergone spinal anesthesia before. The technique of being put under anesthesia was accepted by her, and there was no antecedent neurological disease. The difficulty in the performance of lumbar puncture is not easily explained. Inexperience (a resident with relatively little experience was assigned to this case), failure to flex the spine adequately in the pregnant woman, and faulty selection of body landmarks were probably responsible. The ache in the back at the puncture site, the experience of multiple paresthesias, particularly in the left leg, which subsequently was most severely involved, and the recovery of blood-stained cerebrospinal fluid all suggest a relation to traumatic puncture.

Minor Sequelae of Traumatic Lumbar Puncture

The remainder of the patients had no antecedent neurological disease and no stated objections to spinal anesthesia (see table). There were several more women than men. Tetracaine-dextrose solution was the anesthetic used in 13 of the 17 patients.

The common denominator in all of these cases was the multiple insertion of the lumbar-puncture needle with the production of paresthesias in the lumbar and sacral dermatomes. Blood-stained fluid was seen only once. In all patients subsequent complaints, whether of pain, paresthesia, or numbness, could be related to the paresthesia experienced at the time of lumbar puncture. The duration of postanesthetic complaints ranged from one day to many months. Symptoms were never incapacitating or progressive. It is not surprising that objective signs of neurological disease should be absent since trauma must have involved relatively few fibers in the nerve roots.

Some characteristics of the pain deserve mention. As is often the case, exacerbation of pain was frequently associated with damp weather or certain bodily positions. The symptoms in cases 7, 10, and 14 bear resemblance to the syndrome of meralgia paresthetica which we have previously discussed as a possible residual of spinal anesthesia.[1b] Case 10 was unusual in that pain and paresthesias were experienced in the shoulder girdle at the time of lumbar puncture. This symptom has been noted before as Lhermitte's sign, which in this case may be ascribed to a reduction in spinal fluid pressure producing traction on adhesions or other mechanical factors at higher levels of the spinal cord.[7]

Comment

The cases herein described represent a group different from those reported by us before. Inept lumbar puncture in these cases as a part of spinal anesthesia was followed by neurological signs and symptoms. In one patient (case 2) the signs and symptoms that followed were alarming while in the majority only transient discomfort was produced. In none was antecedent neurological disease a factor. The eventual complete recovery in every patient suggested transient damage such as may occur after trauma. Trauma was also suggested by the factors of multiple needle insertion, the production of back pain and paresthesias, and the occasional recovery of blood-stained spinal fluid. We doubt that an intraneural or intraspinal injection was made in any patient since these are usually associated with excruciating paresthesias at the time of injection, frequent loss of consciousness, and the onset in the immediate postoperative period of permanent sensory and motor defect due to spinal cord destruction.

Some of the complaints may have been the result of damage to the deeper tissues of the back and the establishment of chronic foci for the production of pain. Trauma to ligaments, fascia, or bone with production of localized hemorrhage can give rise to classic low-back pain and sciatic radiation. The syndrome can be produced experimentally on injection of hypertonic saline into the tissues of the back[8] or on injury to the ligaments of the intervertebral disk.[9] Protruded disk as a sequel of traumatic lumbar puncture has also been reported.[6] It is likewise possible that injury to the nerve roots in the cauda equina may have caused a radiculitis not extensive enough to be corroborated by sensory neurological deficit. Still another possibility may have been the onset of a sterile inflammatory reaction brought about by the introduction of blood which we did not detect into the subarachnoid space.[10] Consulting neurologists were unable to help in the elucidation of any of these problems.

The potential trauma of lumbar puncture was vividly depicted in 1944 by Dickson,[11] who stated that "in the centrifugalized deposits of lumbar-puncture specimens, I have not infrequently encountered squamous cells from the skin-surface, together with their accompanying staphylococci, etc., and occasionally even a little cylindrical fragment of skin punched out by the exploring needle." He also reported the presence of myelocytes and nucleated red blood cells, presumably caused by injury to bone marrow, as well as that of cartilaginous cells from the intervertebral disk, which resulted from needling this structure.

Obviously not all traumatic lumbar punctures need result in neurological complaints. Paresthesias are not entirely preventable even by experienced hands. Paresthesias have been encountered during lumbar puncture in 13% of a large series of patients in whom spinal anesthetics were used with the single dose technique and in 30% of patients in whom catheter was used for continuous injections of spinal anesthetics, yet few patients subsequently suffered any form of disability.[12] We believe, however, that lumbar puncture can be performed with little trauma if a planned approach is used. The proper approach to the use of spinal anesthetics lies in the intelligent selection of patients and the examination of the spine in the preanesthetic period. The patient with marked obesity, spinal curvature, or arthritis may then be given another form of anesthetic. If not, attention may be paid to special positions and techniques which will make the lumbar puncture easier to perform. The patient must be in the most advantageous position, and an assistant should be available to provide maximum flexion of the spine and to support the patient. The common practice of aimless insertion of the needle in several directions must be avoided. When difficulty is encountered with a midline insertion, an alternate technique of puncture, such as the lateral approach, may be tried. Blood-stained cerebrospinal fluid must be allowed to clear completely before injection of the local anesthetic. Injection should never be made in the presence of persistent paresthesia lest the injection be made into a nerve root or into the spinal cord. In this situation the needle should be inserted in another position or at another interspace. Finally the question will always arise as to when to abandon lumbar puncture. It is not easy to adopt an objective viewpoint in the midst of a technical procedure performed just before operation. Blind persistence is totally unwarranted and unjust. If a technique other than spinal anesthesia can be safely applied, and it usually can be, the patient must be spared further discomfort and possible complications such as have been described in this report.

Summary

The practice of producing spinal anesthesia does not deserve the objections raised against it. The method is one of great potential value for many patients. Its proper application involves attention to certain details of technique which have been clearly stated in the past but which apparently require reemphasis.

This paper constitutes a plea for a meticulous technique in the performance of lumbar puncture, not only during spinal anesthesia but also for diag-

nostic purposes. Possible causes of the development of neurological symptoms after traumatic lumbar puncture include production of a focus of pain in the tissues of the back, onset of traumatic radiculitis, and development of aseptic hemogenic meningitis. While paresthesias cannot always be avoided during lumbar puncture, proper selection of patients for spinal anesthesia and attention to certain well-known details in technique will largely eliminate trauma. Spinal anesthesia should be abandoned before lumbar puncture reaches the traumatic stage, and another technique of anesthesia should be chosen.

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FILMHOLDER FOR PERSONNEL MONITORING.—In order to evaluate the dose of ionizing radiation from films used to monitor personnel liable to be exposed, the quality of the effective radiation must be determined from the film, since the response of the emulsion varies with quality. With the filmholders used up to now, quality has been assessed from the absorption in the metal filters covering the film wrapper. Contrast methods of this kind, however, suffer from basic limitations. . . . (1) Contrast is an unreliable criterion of quality, and lack of contrast, as often produced by very hard γ rays, makes discrimination from fogged films impossible. (2) β particles and soft diagnostic X-rays cannot be distinguished from each other. (3) No inference on direction of the effective radiation can be made. . . . Taking a wider view on the approach to film monitoring methods, the use of absorption measurements for the characterisation of radiation ought to be abandoned wherever possible. Too many ill-defined factors make apparent absorption an unreliable indicator of quality. . . . Other means besides absorption, such as electron emission from metal foils or type of scatter produced by the radiation, frequently offer quality discrimination where absorption measurements fail, particularly with mixed radiation. To assess less energetic back-scatter without interference from the front, the front filter at the particular region must act as blocking filter. . . .

In 1950 one of the authors (G. S.) described a method of quality discrimination based on the electron emission from metal foils in contact with the film, which provides satisfactory discrimination for energies up to 2 MeV. Since it is practically impossible to accommodate metal foils within the wrapper, the authors have now devised a holder on which a lead foil is used outside the wrapper as emitter of secondary electrons. Although this arrangement reduces energy discrimination, the new holder eliminates most of the serious shortcomings inherent in the old methods which relied entirely on absorption data.—G. Spiegler and R. Davis, An Improved Method and Filmholder for Personnel Monitoring, *The British Journal of Radiology*, July, 1959.

POSTOPERATIVE NAUSEA AND VOMITING

III. EVALUATION OF THE ANTIEMETIC DRUGS FLUPHENAZINE (PROLIXIN) AND PROMETHAZINE (PHENERGAN) AND COMPARISON WITH TRIFLUPROMAZINE (VESPRIN) AND CYCLIZINE (MAREZINE)

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A double-blind study was made to test the comparative value of four antiemetic drugs in preventing postoperative nausea and vomiting. A total of 3,454 patients were studied. Of these, 1,114 received nothing, 367 received a placebo, 754 received triflupromazine, 537 received cyclizine, 442 received fluphenazine, and 240 received promethazine. It is probable that there was no placebo response in these studies, since most of the patients were unconscious when the test drug was administered. Cyclizine was more effective than the placebo, but the phenothiazine compounds were significantly more effective than either in reducing the percentage of awake patients who reported nausea. Promethazine and triflupromazine significantly prolonged postanesthetic sleep. Unlike doses of fluphenazine and promethazine, doses in excess of 7.5 mg. of triflupromazine produced significant hypotensive side-effects.

Postoperative nausea and vomiting is a frequent complication of anesthesia and surgery. Many compounds recommended for the treatment of this condition have been only casually studied, and little information on several compounds studied under similar conditions of control is available. To gain more insight into this problem as it exists at Memorial Center, we set up a controlled study in January, 1958. This report summarizes our results with various doses of the four compounds studied.

Method

The method used has been described in a previous report.[1] In essence it consisted of a balanced, double-blind, random study in which all the drugs were administered as agents unknown to the nurse and patient. Subjects were selected from those patients whose surgeons had given permission for the prophylactic treatment of postoperative nausea and vomiting. They were further selected in that patients below 14 years of age and those who had complications during the anesthesia or surgery were excluded.

On their arrival in the recovery room, selected patients received an injection of 1 ml. of the unknown drug in the deltoid muscle. The influence of variables such as anesthetic agent and intra-abdominal or extra-abdominal surgery were further controlled by classifying the patients in one of six categories, depending on the type of anesthetic used and the operation performed. Randomization of the order of drug administration within these six categories was another essential to balance out variables otherwise uncontrolled in the experimental design. A special nurse administered the test medicament on the patient's arrival in the recovery room, observed him every half hour, and scored the nausea or vomiting as follows: no nausea, nausea, retching, or vomiting. This information was entered on a study card along with information pertinent to the patient's medical history, anesthesia, operation, and postoperative course. Later the data on these study cards were transferred to IBM punch cards.

In the first phase of this controlled study the patients received one of five regimens: either a placebo, 50 or 100 mg. of cyclizine (Marezine), or 15 or 30 mg. of triflupromazine (Vesprin). Later, triflupromazine was studied, at the 7.5 and 15 mg. dose level, along with 50 and 100 mg. of cyclizine and placebo.[2] During the second phase of the study, which is the basis for the body of this report, patients received 7.5 mg. of triflupromazine, 12.5 or 25 mg. of promethazine (Phenergan), or 4 or 8 mg. of fluphenazine (Prolixin). Later fluphenazine was studied at the 2 and 4 mg. dose level, along with the other medicaments. At the same time a control group who received no antiemetic medication was studied. Patients in the control group met all the criteria applied to those who received the study medicaments except that the permission of their attending surgeon for prophylactic medication was not asked.

Results

A total of 3,454 patients was studied. Of these, 1,114 were controls, 367 received a placebo, 754 received triflupromazine, 537 received cyclizine, 442 received fluphenazine, and 240 received promethazine. The effect of these medicaments on the incidence of nausea and vomiting is shown in figure 1. No significant difference was found between the

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group who received the placebo and those who received no medicaments; thus they were considered as a unit for purposes of statistical analysis. The incidence of nausea and vomiting in the control group was 17.5%, in the placebo group 18.5%, and in the combined group 17.8%. Administration of fluphenazine, promethazine, and triflupromazine produced a marked and significant reduction in the incidence of nausea and vomiting to less than 5%. Although the incidence of nausea and vomiting varied among these three drug groups, there is no significant difference among them when the means for the drug groups are compared. When the drugs are analyzed on a dose-response basis, administration of 25 mg. of promethazine produced better results than 12.5 mg. (2.4 and 6.2% respectively), although this difference was not statistically significant. Among the patients in this study who received fluphenazine, 2, 4, or 8 mg., the incidences of nausea and vomiting were 3.5, 4.4, and 3.8% respectively. Again, as previously reported,[2] no statistically significant difference was detected among the three dose levels of triflupromazine, 7.5, 15, and 30 mg., when incidence was considered (6.0, 3.2, and 5.4% respectively). The results with cyclizine therapy, which reduced the incidence of nausea and vomiting to a significant extent, are also shown in figure 1. There was no significant difference between the incidence of nausea and vomiting after administration of 50 mg. as compared with 100 mg. of cyclizine.

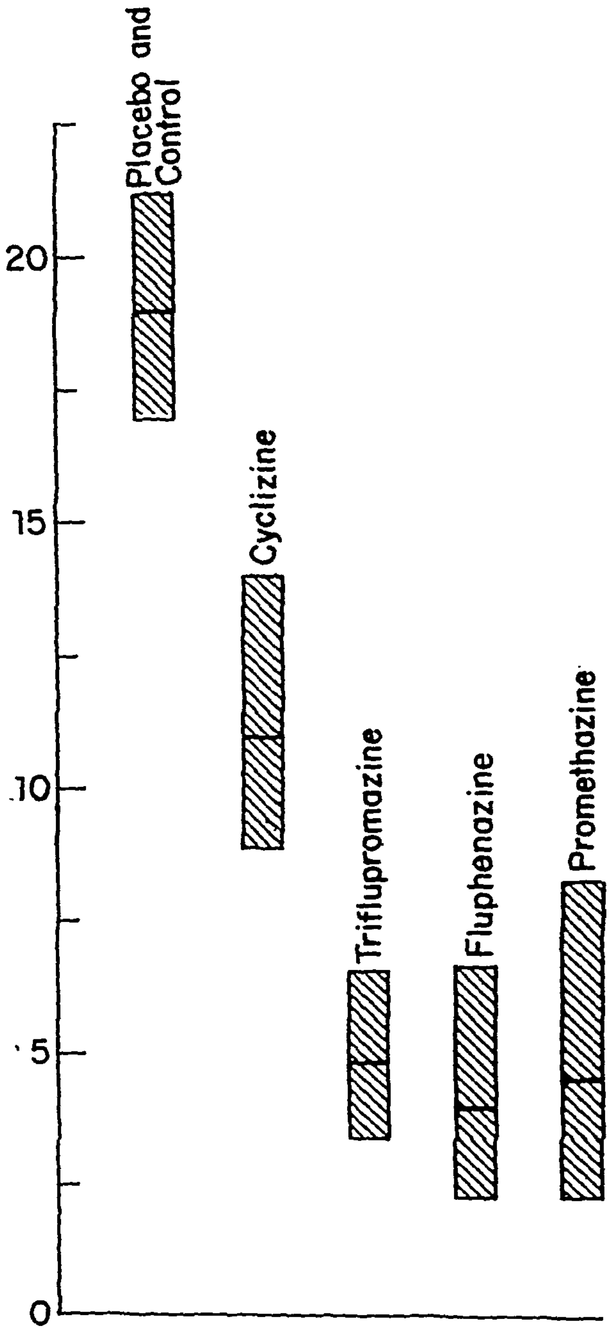

Fig. 1.—Mean incidence of nausea and vomiting. Cross-hatched area indicates 95% confidence limits.

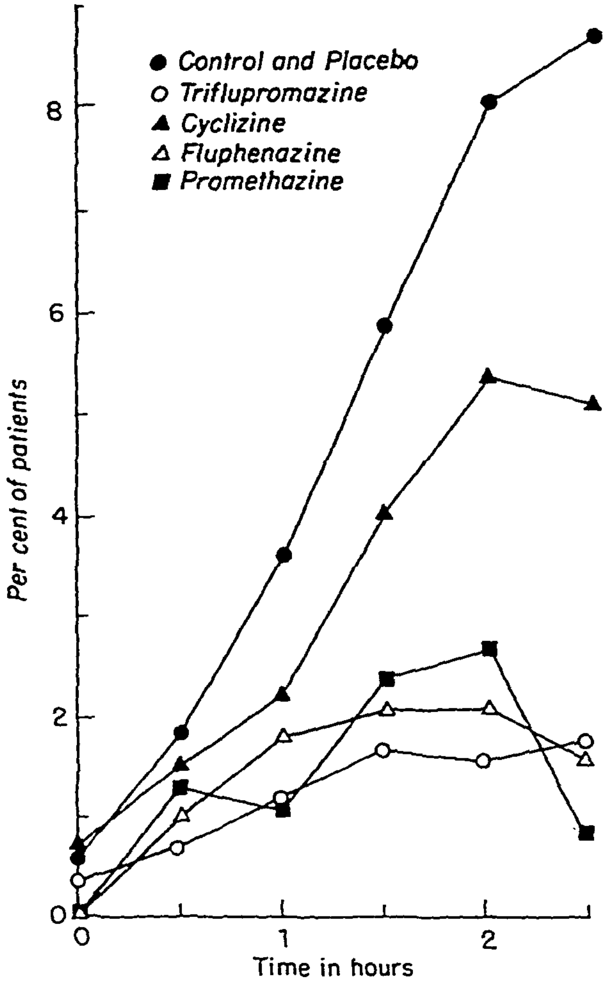

Fig. 2.—Percentage of awake patients reporting nausea at any one observation period.

The percentage of awake patients nauseated at any one time was also analyzed (fig. 2). The percentage of awake patients nauseated in the placebo group increased almost linearly up to two hours. The curve for patients after therapy with cyclizine probably for others, the antiemetic action is independent of sedative effects. This observation would cast doubt on the proposal [5] to use the apomorphine test as a screening procedure for tranquilizing agents, since these two pharmacological properties seem to be independent in this case.

Hypotension has been reported to occur after the administration of phenothiazine derivatives. In the clinical studies we have conducted we have found clinically significant hypotension only after triflupromazine had been given. It appeared to be directly related to dosage, since hypotensive effects of 7.5 mg. could not be distinguished from those of placebo, whereas 15 and 30 mg. produced significant hypotension.[2] Under the conditions of our study, administration of 12.5 and 25 mg. of promethazine did not produce hypotension considered clinically significant. This is consistent with the data of Millar [6] but not with the data of Eckenhoff and associates [7] who demonstrated significant hypotension after 50 mg. of promethazine had been given. It may be that the hypotensive effects of promethazine are a function of dosage, as was our experience with triflupromazine, and in our study would be demonstrable at the 50 mg. dose level, too. However, it may be that the tilt table technique may be capable of detecting hypotensive effects that would not be apparent in our clinical situation.

The likelihood that untoward side-effects will occur after the use of a single injection of the phenothiazine compounds for treatment of postoperative nausea and vomiting is small. Significant hypotension was not seen with administration of up to 8 mg. of fluphenazine and with 7.5 mg. of triflupromazine or 25 mg. of promethazine. Sedative effects were seen after giving promethazine and triflupromazine, but not after administration of fluphenazine. Transitory extrapyramidal symptoms were not seen in any patient in this study. This may be because the residual sedative effect of the anesthetic prevents these symptoms. However, we have seen extrapyramidal symptoms consisting of oculogyric crises after administration of a single dose of 5 mg. of fluphenazine to an ambulant subject. These symptoms responded to appropriate sedative therapy. Darling [8] has reported the frequent occurrence of extrapyramidal symptoms after the use of fluphenazine. Whether these symptoms are more frequent after the administration of this particular phenothiazine than others remains to be determined.

Summary and Conclusions

Fluphenazine (Prolixin) and promethazine (Phenergan) are effective antiemetic agents. In comparison with results obtained previously with administration of cyclizine (Marezine) and triflupromazine (Vesprin) they appear to be more effective than cyclizine and as effective as triflupromazine. In contrast to triflupromazine, clinically significant hypotensive side-effects were not seen after giving fluphenazine and promethazine in the dosage studied.

A controlled, double-blind study was set up to study the effectiveness of these drugs in prophylactic treatment of postoperative nausea and vomiting. Selected patients, on arrival in the recovery room, received 1 ml. of a coded test drug intramuscularly and were carefully observed for 2½ hours by a full-time nurse observer. In the group of patients who received a placebo the incidence of nausea and vomiting was 18.5%. Cyclizine and triflupromazine which were studied initially reduced this incidence to about 11 and 5% respectively. In this study, giving fluphenazine and promethazine reduced the incidence to about 4%. Hypotensive side-effects were also evaluated. Significant prolongation of postanesthetic sleeping time was noted after giving promethazine but not after giving fluphenazine.

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TABLE 2.—*Distribution by Percentage of Certain Variables Among Patients Treated with Drugs*

		Cyclizine		Triflupromazine			Promethazine		Fluphenazine		
Categories	Placebo	50 Mg.	100 Mg.	7.5 Mg.	15 Mg.	30 Mg.	12.5 Mg.	25 Mg.	2 Mg.	4 Mg.	8 Mg.
Female	69.5	65.4	67.1	69.7	66.2	69.0	69.5	75.6	65.5	76.7	74.1
Caucasoid	97.8	95.8	97.4	97.8	99.0	95.3	98.4	96.9	98.2	96.8	97.6
Obese	16.6	19.4	15.0	14.2	14.6	26.4	6.2	8.7	5.3	8.8	11.8
"Normal"	78.7	75.7	77.4	82.3	79.9	67.4	87.5	82.7	92.9	84.2	83.5
Thin	4.6	4.9	7.7	3.5	5.2	6.2	5.3	7.9	1.8	6.9	4.1
Ether	28.3	26.2	25.5	27.4	25.6	34.1	35.1	33.1	31.0	33.3	32.4
Cyclopropane	21.0	21.7	23.0	16.1	20.4	27.1	13.2	12.6	17.7	13.8	13.0
Thiopental $+N_2O$	50.1	50.6	50.4	55.2	50.9	38.7	50.0	51.2	46.9	52.2	54.1
Intubated	45.2	41.8	45.3	42.3	43.5	50.4	46.9	37.8	46.0	40.9	47.1
Intra-abdominal	22.3	20.1	16.0	18.3	18.8	21.7	13.3	15.0	15.0	18.9	15.3
Morphine	18.5	16.7	17.5	20.2	20.4	8.5	19.5	29.1	29.2	28.3	21.8
Meperidine	79.6	79.1	79.6	77.6	76.9	88.4	77.3	69.3	69.9	69.2	77.1
Barbiturate	62.9	66.5	61.7	54.2	57.8	71.3	32.1	35.4	39.8	40.9	36.5
Scopolamine	91.0	87.8	87.2	91.8	85.4	81.5	93.7	94.5	96.5	97.5	96.5
Atropine	9.3	11.8	12.8	8.2	12.3	14.7	5.5	4.7	2.7	2.5	2.9
Av. age, yr.	49.4	50.0	49.9	49.9	50.5	49.2	51.5	49.6	49.1	49.4	48.9
Av. wgt., kg.	66.8	66.1	61.2	66.1	64.3	67.7	64.8	64.8	67.7	65.6	66.4
Patients	367*	263*	274*	317*	308*	129*	128*	127*	113*	159*	170*

*Total number of patients in each category.

The cyclizine used in this study was supplied as Marezine by Burroughs Wellcome and Co. (U. S. A.) Inc., Tuckahoe, N. Y. The triflupromazine used in this study was supplied as Vesprin and the fluphenazine as Prolixin by E. R. Squibb and Sons, New York. The promethazine used in this study was supplied as Phenergan by Wyeth Laboratories, Philadelphia.

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COMPARISON OF TOXICITY OF INTRAVENOUSLY GIVEN LOCAL ANESTHETIC AGENTS IN MAN

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Twelve unanesthetized volunteers received intravenous infusions of procaine, chloroprocaine, tetracaine, and lidocaine to permit comparison of the systemic toxic effects of the drugs. Administration by vein assured equivalent plasma level of the agents and permitted a controlled dosage simulating one ordinarily used for regional anesthesia. The resulting functional disturbances were relatively minor, yet electrocardiographic tracings indicative of deteriorating cardiac activity were frequently encountered. The electroencephalographic tracings simulated the pattern of those of a person when normally asleep. The spikes typically seen in EEG tracings just before epileptic seizures were absent on the records of two subjects who had convulsions. Lidocaine was most poorly tolerated. Chloroprocaine was tolerated the best, and its low toxicity is considered to be due to its more rapid hydrolysis by plasma cholinesterase.

Whatever their route of administration, in the final analysis, the toxicity of local anesthetic agents depends on their plasma[1] concentration. Because of the influence of various factors (e. g., permeability through tissue-blood barriers) on the plasma level of local anesthetic agents, after other than intravenous administration, the latter route is the most suitable for the study of the toxicity of these compounds.

The toxicity of the commonly used local anesthetic agents when intravenously given has been adequately studied in various laboratory animals.[2] Despite the fact that local anesthetic agents have been widely used for the treatment of various pathological conditions[3] in unanesthetized human subjects and for the supplementation of anesthesia[4] and the decrease of cardiac irritability[5] in anesthetized patients, no quantitative data are available on their toxicity when intravenously administered in man.

Because of marked quantitative differences in the enzymatic breakdown of the ester type of local anesthetic agent, in various laboratory animals on one hand and in man on the other,[6a] the results of pharmacological studies on the intravenous toxicity of local anesthetic agents obtained in animals cannot be applied to man. Human plasma hydrolyzes procaine and other ester-type local anesthetic agents 4 to 20 times faster than that of different laboratory animals.[6b] Consequently, rate of hydrolysis is of relatively little significance in the disposition of the ester-type local anesthetic agents in those

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mammals on which their intravenous toxicity is usually tested. Since hydrolysis by plasma esterases plays no role in the determination of the plasma level of the nonester type of local anesthetic agent, any comparison of the intravenous toxicity obtained in laboratory animals will be relatively favorable to these agents. Because of this, in man the relative toxicity of hydrolyzable local anesthetic agents should be less than that of the nonhydrolyzable agents in comparison to that in other mammals. In agreement with these considerations, the incidence, duration, and severity of systemic reactions encountered with the clinical use of local anesthetic agents have been much less with the rapidly hydrolyzable agents than with those which are not at all or only slowly hydrolyzed by plasma esterases.[7] This marked difference in the role of enzymatic breakdown in the disposition of the hydrolyzable and nonhydrolyzable local anesthetic agents in man and other mammals prompted the study of the intravenous toxicity of local anesthetic agents in man. It has been the purpose of this investigation to obtain quantitative data in man on the relative toxicity of three commonly used local anesthetic agents hydrolyzed by plasma esterases and one other which is not affected by these enzymes.

TABLE 1.—*Tolerated Duration of Infusion and Time of Onset and Disappearance of Signs and Symptoms After Intravenous Administration of Local Anesthetic Agents*

Agent,	Mg./Kg./Min.	Cases, No.	Duration of Infusion, Min.	Time of Onset of Symptoms After Start of Infusion, Min.	Time of Disappearance of Symptoms After End of Infusion Min.
procaine hydrochloride ...	1.0	10	19.2 ±1.7[*]	2.8±0.3	12.3 ±2.8
2-chloroprocaine hydrochloride	1.0	10	22.8 ±1.3	3.0±0.4	4.7[†]±1.3
tetracaine hydrochloride ..	0.125	10	20.1 ±1.6	5.1±1.6	11.9 ±2.8
lidocaine hydrochloride	0.5	10	12.8[†]±1.1	2.8±0.3	18.5 ±3.2

[*] Standard error.
[†] Statistically significant.

Experimental Procedure

The investigation was carried out on 12 healthy male volunteers from 21 to 35 years of age. The local anesthetic agents investigated were procaine hydrochloride, chloroprocaine (Nesacaine) hydrochloride, tetracaine (Pontocaine) hydrochloride, and lidocaine (Xylocaine) hydrochloride. Each agent was infused intravenously, by means of a Harvard 600-900 variable speed infusion pump at the rate of 4 ml. per minute. The concentrations of the local anesthetic agents were so adjusted that 4 ml. contained 1.0 mg. of procaine of chloroprocaine, 0.5 mg. of lidocaine, or 0.125 mg. per kilogram of body weight of tetracaine. With the exception of chloroprocaine hydrochloride, which was administered at one and one-half times the corresponding rate, the milligram per kilogram of body weight per minute doses were so selected that their ratio corresponded to the ratio of the concentrations in which they are generally used for regional anesthesia. The reason for administering chloroprocaine hydrochloride at one and one-half times the corresponding rate had been to determine if the claims made for its relatively low systemic toxicity,[7] could be substantiated under controlled circumstances.

The subjects served as their own controls and with few exceptions received, at weekly intervals, intravenous infusions of all four agents. Blood pressure, pulse, and respiratory rates were recorded, and lead 2 electrocardiogram and left occipitofrontal electroencephalogram tracings were made with a cardioencephalograph before the start and every two minutes thereafter until the conclusion of the experiment. The subjects were also observed for signs of increased cortical irritability (e. g., muscle fasciculations, twitchings, convulsions) and were questioned at two-minute intervals to ascertain changes in cerebration and to obtain information on subjective changes such as numbness in extremities or lips, sensation of twitching, difficulties in breathing, speaking, swallowing, blurred or double vision, inability to distinguish between colors, dizziness, and sensation of cold.

The administration of the local anesthetic agents was discontinued after 25 minutes or earlier if generalized twitchings, convulsions, severe breathing difficulties, loss of consciousness or total disorientation developed. Beside the duration of the intravenous infusion of the local anesthetic agents, the time from the end of infusion time to the disappearance of all signs and symptoms of toxicity was also noted. The hydrolysis rates of the three ester-type agents were determined in heparinized plasma obtained from each subject before and in some cases after the end of infusion.

The plasma levels of p-aminobenzoic acid and p-amino-2-chlorobenzoic acid were measured in venous blood samples drawn at the termination of the infusion of procaine and chloroprocaine hydrochloride, respectively, by the Bratton-Marshall method.[8] The lidocaine hydrochloride concentrations in venous blood were also measured by a modification of the method of Sung and Truant.[9]

TABLE 2.—*Hydrolysis Rates and Plasma Levels of Breakdown Products After Infusion of Ester-Type Local Anesthetic Agents*

Agent	Hydrolysis Rate, μ mole Ml./30 Min.	p-Aminobenzoic Acid Concentration, Mcg./Ml.
Procaine hydrochloride ..	0.52±0.04[*]	4.74±0.59
2-Chloroprocaine hydrochloride	2.12±0.25	31.58±2.87
Tetracaine hydrochloride.	0.15±0.01	......

[*] Standard error.

Four subjects also received intravenously given sodium p-aminobenzoate at the rate of 0.58 mg. per kilogram of body weight per minute for the same length of time as the duration of their procaine infusion. The rate of infusion of sodium p-aminobenzoate was so selected that the corresponding quantity of p-aminobenzoic acid would equal that obtained from the complete hydrolysis of procaine hydrochloride administered at the rate of 1.0 mg. per kilogram of body weight per minute.

At all times, three physicians, trained in resuscitation, were present during the experiments. Drugs and equipment for the management of convulsions and respiratory or circulatory arrest were also kept in readiness.

Results

The intravenous administration of all four local anesthetic agents caused a variety of signs and symptoms which in most cases necessitated termination of the experiment before the end of the arbitrarily chosen 25-minute period. The figures of table 1 indicate that, at the rates selected, the intravenous infusion of chloroprocaine hydrochloride was tolerated the best and that of lidocaine hydrochloride the least well. The duration of the tolerated length of infusion with lidocaine hydrochloride was significantly shorter (t between procaine and lidocaine equals 3.7; $p<0.01$) than with the three hydrolyzable agents. The intravenous infusion of procaine, chloroprocaine, and tetracaine hydrochloride were tolerated for the full 25 minutes in 3 of 10, 10 of 12, and 4 of 10 patients respectively. None of the 10 subjects tolerated the infusion of lidocaine hydrochloride for more than 18 minutes.

TABLE 3.—*Percentage of Subjects in Whom Circulatory and Respiratory Changes* Occurred after Intravenous Infusion of Local Anesthetic Agents*

	Pulse Rate			Blood Pressure			Respiratory Rate			Electrocardiographic Changes	
Agent	Increased	Decreased	No Change	Increased	Decreased	No Change	Increased	Decreased	No Change	Present	Absent
Procaine hydrochloride ..	80	10	10	50	30	20	50	10	40	80	20
2-Chloroprocaine hydrochloride	42	16	42	33	8	59	59	0	41	41	59
Tetracaine hydrochloride .	70	0	30	30	10	60	30	30	40	30	70
Lidocaine hydrochloride .	80	10	10	90	0	10	30	40	30	30	70

* Only changes of pulse and respiratory rates and blood pressure greater than ± 10% of control value were considered.

There was no marked difference in the time of onset of signs and symptoms between the four agents studied. Signs and symptoms, however, disappeared significantly faster after administration of chloroprocaine hydrochloride (t between procaine and chloroprocaine equals 2.6; $p<0.05$) than the other three agents and persisted the longest after lidocaine.

In agreement with previous findings,[10] chloroprocaine hydrochloride was hydrolyzed by the plasma of our subjects about four times faster and tetracaine hydrochloride about three and one-half times slower than procaine (see table 2). There was no significant difference in hydrolysis rate between the plasma obtained before and that obtained after the infusion of local anesthetic agents. Because of the more rapid enzymatic hydrolysis of chloroprocaine, the concentration of its breakdown product, p-amino-2-chlorobenzoic acid was about seven times higher (31.58±2.87 mcg. per milliliter) in the plasmas obtained at the termination of the experiment than those of p-aminobenzoic acid (4.74±0.59 mcg. per milliliter) determined under identical circumstances after the infusion of procaine. The p-aminobenzoic acid levels after the infusion of tetracaine hydrochloride were too low for the sensitivity of available methods to detect. For the same reasons the determination of the procaine and chloroprocaine hydrochloride concentrations at the termination of the experiments also had to be abandoned. The lidocaine plasma levels at the termination of the infusion were 5.29±0.55 mcg. per milliliter of plasma. The average plasma concentration of p-aminobenzoic acid after the intravenous infusion of 0.58 mg. per kilogram of body weight per minute of sodium p-aminobenzoate for 13 to 25 minutes was 54.70±7.16 mcg. per milliliter.

The incidence of circulatory and respiratory changes are summarized in table 3. Only changes greater than ±10% of control values were considered. The administration of the local anesthetic agents caused an increase of pulse rate in 70 to 80% of the subjects after procaine, tetracaine, and lidocaine and in 40% in those receiving chloroprocaine hydrochloride. A decrease of pulse rate was not at all, or infrequently, encountered with all four agents. Similarly, systolic blood pressure had a tendency to rise or remain unchanged. The incidence of moderate elevation of blood pressure was greatest with lidocaine (90%), and the lowest with chloroprocaine and tetracaine hydrochloride (30%). After use of procaine, elevation of blood pressure was encountered in 50 and fall of blood pressure in 30% of subjects. With use of procaine and chloroprocaine hydrochloride increased and with use of lidocaine hydrochloride decreased respiratory rates were frequently encountered. The incidence of increased and decreased respiratory rates was about the same with use of tetracaine hydrochloride.

Changes in the electrocardiographic pattern included flattening or disappearance of the T wave, depression of the S-T segment (fig. 1A), and occasionally an increase in the amplitude of the P wave (fig. 1B). These changes were encountered most frequently after the intravenous infusion of procaine (80%). The incidence of electrocardiographic change was 30 to 41% with the other three agents used. The electrocardiographic changes disappeared most rapidly after discontinuation of the intravenous infusion of chloroprocaine hydrochloride.

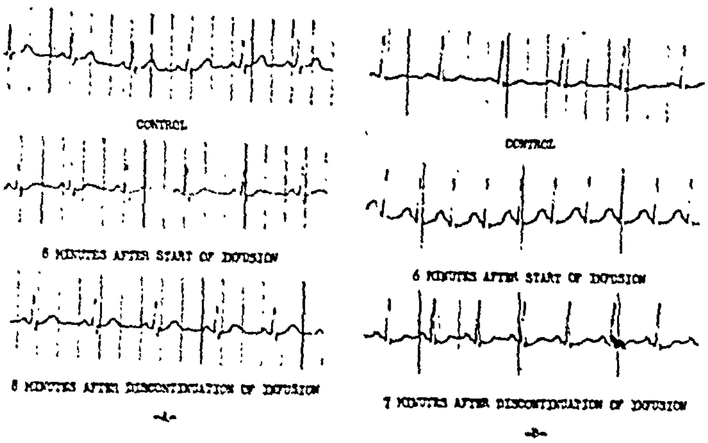
CONTROL
8 MINUTES AFTER START OF INFUSION
8 MINUTES AFTER DISCONTINUATION OF INFUSION
-A-
CONTROL
6 MINUTES AFTER START OF INFUSION
7 MINUTES AFTER DISCONTINUATION OF INFUSION
-B-

Fig. 1.—Electrocardiographic changes after intravenous infusion of procaine. *A*, note depression of S-T segment and flattening of T wave eight minutes after start of infusion and return of preinfusion pattern eight minutes after discontinuation. *B*, note tachycardia and increase in height and width of P wave six minutes after start of infusion and return of preinfusion pattern with persistent tachycardia seven minutes after discontinuation.

The most striking features of the electroencephalographic changes were the disappearance of the alpha waves and the manifestation of slow activity, with the development of theta and delta waves indicating suppression of cortical activity similar to that seen in sleep (fig. 2). The typical spikes which usually accompany cortical irritability, as seen in epilepsy, were not encountered in any of our subjects, two of whom developed frank convulsions. In both of these patients, alpha waves reappeared a few minutes prior to the start of convulsions and gave place to theta and delta waves after the administration of thiopental sodium. Electroencephalogram patterns also returned to normal most rapidly after discontinuation of the intravenous infusion of chloroprocaine hydrochloride.

Signs of cortical irritation manifested by visible muscular fasciculations or twitchings were present in all subjects who received lidocaine and, with one exception each, in all of those who received procaine or tetracaine hydrochloride. Only 7 of the 12 patients who received infusions of chloroprocaine hydrochloride developed fasciculations or twitchings. Generalized convulsions were encountered in one subject after the intravenous infusion of tetracaine and in one after that of lidocaine hydrochloride. These subsided promptly after the intravenous administration of 200 to 250 mg. of thiopental sodium.

Other objective signs, present with variable frequency with all agents, included dysarthria, disorientation, sweating, and euphoria. Euphoria was seen most frequently with use of lidocaine hydrochloride. The subjective symptoms included sleepiness; confusion; numbness of extremities, face, or whole body; visual disturbances such as blurring, diplopia, or color blindness; sensation of cold; lump in the throat; and heaviness in the chest. The subjects frequently complained of a sensation of twitching in the extremities or diaphragm before any objective signs of muscle irritability could be seen.

Both symptoms and signs disappeared most rapidly (less than 5 minutes) after use of chloroprocaine hydrochloride and most slowly (about 18½ minutes) after use of lidocaine (see table 1). With administration of tetracaine and lidocaine hydrochloride the intensity of signs and symptoms frequently increased for a few minutes after the discontinuation of the infusion. The intravenous infusion of sodium p-aminobenzoate caused no signs or symptoms in any of the four subjects.

Comment

The findings presented indicate that despite the fact that it was administered at a relatively higher rate than the other three local anesthetic agents investigated, the intravenous infusion of chloroprocaine hydrochloride was tolerated the best. This low systemic toxicity of chloroprocaine is due to the fortuitous circumstance that although its clinical potency is considerably higher than that of procaine, it is hydrolyzed four to five times faster by plasma cholinesterase than the latter compound. Because of this rapid enzymatic breakdown, chloroprocaine hydrochloride is the least likely agent to accumulate to toxic concentrations in human plasma after its parenteral administration. The finding

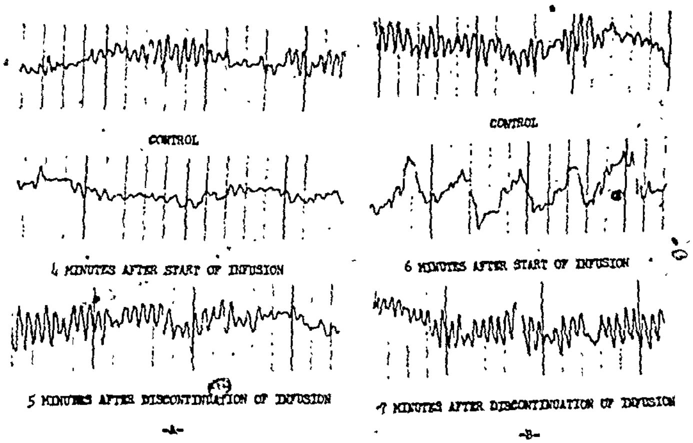
CONTROL
4 MINUTES AFTER START OF INFUSION
5 MINUTES AFTER DISCONTINUATION OF INFUSION
-A-
CONTROL
6 MINUTES AFTER START OF INFUSION
7 MINUTES AFTER DISCONTINUATION OF INFUSION
-B-

Fig. 2.—Electroencephalographic changes after intravenous infusion of procaine and chloroprocaine. *A*, note disappearance of alpha waves and replacement by theta waves four minutes after start of infusion of chloroprocaine and return of control pattern five minutes after discontinuation of infusion. *B*, note replacement of alpha waves of control tracing by predominantly delta waves six minutes after start of infusion of procaine and return of alpha waves seven minutes after discontinuation of infusion.

that about seven times as much p-aminobenzoic acid was present in the plasmas of our experimental subjects after the infusion of chloroprocaine than after that of the corresponding amounts of procaine, confirmed in vivo the in vitro observation of more rapid hydrolysis of chloroprocaine hydrochloride. The significantly higher plasma p-aminobenzoic acid level observed after the intravenous administration of chloroprocaine hydrochloride may be explained by the assumption that the more hydrophilic p-aminobenzoic acid passes the blood-tissue barriers less readily than the more lipophilic procaine or chloroprocaine hydrochloride. This assumption is corroborated by the finding that the intravenous administration of sodium p-aminobenzoate results in more than 10 times higher plasma concentration of p-aminobenzoic acid than that observed after the infusion of corresponding quantities of procaine. While the slowly hydrolyzable procaine has ample opportunity to leave the blood stream, more of the rapidly hydrolyzable chloroprocaine hydrochloride breaks down in the plasma, with a resultant increase in the p-aminobenzoic acid level and decrease of systemic toxicity. The rapid disappearance of the signs and symptoms of toxicity after discontinuation of the infusion of chloroprocaine hydrochloride can also be explained by its rapid enzymatic rate of hydrolysis. The relatively low plasma levels of lidocaine (5.29±0.55 mcg. per milliliter) found at the termination of its intravenous infusion indicate that it also diffuses from the blood to other tissues rapidly.

In line with the importance of the rate of hydrolysis to the systemic toxicity of local anesthetic agents, the intravenous toxicity of the more slowly hydrolyzable procaine and tetracaine, and especially that of the nonhydrolyzable lidocaine, was higher than that of chloroprocaine hydrochloride. This was shown primarily by the observation that 10 out of 12 subjects tolerated the infusion of the relatively larger doses of chloroprocaine hydrochloride over the selected 25-minute period and only 7 showed signs of cortical irritation. In contrast, of 10 of these 12 subjects only 3 and 4 tolerated the intravenous infusion of procaine or tetracaine respectively, and none that of lidocaine hydrochloride for the full 25 minutes. All subjects who received lidocaine, and, with one exception in each group, all who received procaine or tetracaine hydrochloride, showed muscular fasciculations and twitchings.

With the exception of the development of convulsions in one subject, tetracaine hydrochloride, under the conditions used, exhibited the same degree of toxicity as procaine. This somewhat unexpected finding might be explained by the fact that while the milligram per kilogram of body weight per minute dose of tetracaine hydrochloride selected on the basis of its clinical potency was one-eighth of that of procaine, it is hydrolyzed by plasma cholinesterase only three to four times slower than the latter.

The general belief that lidocaine hydrochloride is less likely to cause signs of central nervous system irritation than the ester type of local anesthetic agent was not substantiated in this study. The rate of muscular fasciculation was the highest after use of lidocaine, and one subject developed convulsions after its administration. The incidence of euphoria was also highest after administration of lidocaine.

It is of interest that despite relatively minor changes in pulse rate and blood pressure, electrocardiographic signs of deteriorating cardiac activity were encountered relatively frequently after the intravenous infusion of local anesthetic agents. The frequency and intensity of electrocardiographic changes were the highest with use of procaine, considerably lower with chloroprocaine, and the least with tetracaine and lidocaine hydrochloride. This finding should serve as a warning against the indiscriminate intravenous use of local anesthetic agents for the supplementation of intravenously given barbiturates and other general anesthetic agents. While the warning signs of cortical stimulation are usually suppressed by the use of the general anesthetic agents, the depressant effects of these compounds and those of local anesthetics on the myocardium and the vital centers of the central nervous system[11] may be additive. It should be remembered that while lower concentrations of local anesthetic agents decrease the irritability[5b] of the heart, higher concentrations will also interfere with normal conductivity and contractility of the cardiac muscle.

Barring accidental rapid intravenous administration of large quantities of chloroprocaine or the deliberate use of excessive doses in vascular areas (e. g., the sacral canal), without the admixture of epinephrine, systemic reactions to chloroprocaine are unlikely to be encountered except in patients with low plasma cholinesterase levels. In agreement with clinical experience, absorption reactions may be expected to occur more frequently with use of slowly hydrolyzable agents (e. g., procaine or tetracaine) and even more so after the use of nonhydrolyzable agents (e. g., dibucaine, lidocaine). On the basis of these considerations, chloroprocaine should be the preferred agent when large volumes of relatively concentrated solutions of local anesthetic agents must be used. This is especially true in caudal and lumbar epidural block and the conduction anesthesia of large nerve trunks.

The toxicity of local anesthetic agents, not infrequently resulting in serious complications or death, is unfortunately obscured by reluctance to report unfavorable results. In contrast, their advantages are often emphasized out of proportion, and frequently too much reliance is placed on therapeutic indexes obtained from the determination of anesthetic potency and systemic toxicity in animal experiments which cannot be applied to man.

Summary

Procaine hydrochloride and 2-chloroprocaine hydrochloride, 1.0 mg., lidocaine hydrochloride, 0.5 mg., and tetracaine hydrochloride, 0.125 mg. per kilogram of body weight per minute were administered intravenously to 12 unanesthetized human subjects who served as their own controls. The intravenous infusion of chloroprocaine was tolerated the best, and that of lidocaine hydrochloride the least well of the four compounds investigated. After the discontinuation of infusion, the signs and symptoms of systemic toxicity disappeared most rapidly with chloroprocaine and most slowly with lidocaine hydrochloride. Determination of the rates of hydrolysis of the three ester-type local anesthetic agents in the subjects' plasma and measurement of the plasma level of their breakdown products at the termination of the experiments indicated that the low systemic toxicity of chloroprocaine hydrochloride is primarily due to its rapid enzymatic hydrolysis in plasma. The findings of this study confirm the clinical experience that, of the available local anesthetic agents, chloroprocaine hydrochloride is the safest and, consequently, it should be the preferred drug of choice when large volumes of relatively concentrated local anesthetic agents must be used.

1400 Locust St. (19) (Dr. Foldes).

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CHRONIC NEPHRITIS IN CHILDREN.—Persistent microhematuria and proteinuria in childhood may at times be appropriately viewed as indicative of persistent, active nephritis rather than chronic nephritis; the prolonged course is none the less benign, rather than progressive and fatal. The prognosis should be regarded optimistically because of the likelihood that renal healing will be complete. This concept is based on the fact that the condition is associated with normal growth and development and with lack of evidence of progressive renal failure, azotemia and hypertension.—E. C. Burke, M.D., Chronic Nephritis in Children: A Diagnostic Enigma, *Proceedings of the Staff Meetings of the Mayo Clinic,* Dec. 23, 1959.

BUCKING AND BRONCHOSPASM AS PROBLEMS OF ANESTHESIA

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Bucking and bronchospasm are two respiratory disorders that seriously upset the course of anesthesia. Bucking is a violent expiratory contraction of skeletal muscles; bronchospasm is a spastic contraction of the smooth musculature of the bronchial tree. Both are reflex responses to chemical or physical irritations such as accompany the insertion of an endotracheal tube and inhalation of concentrated vapors. Both can be avoided by due care in the administration of general anesthetics and by judicious use of local anesthesia before the insertion of the endotracheal tube. The spray tube here referred to facilitates the renewed application of local anesthetics to the mucosa of the trachea during the subsequent course of the anesthesia. While bronchospasm can be treated by other measures here described, prevention is by all means to be preferred.

The department of anesthesiology at the Medical College of Georgia recently conducted a study[1] with use of a spray-tube, an endotracheal tube with a built-in spray device for topical use of local anesthetic agents. In the course of this study it was learned that bucking by the intubated patient usually could be prevented and, if noticed early, could be stopped by the use of this tube. It was further observed that bronchospasm, once fully established, could not be broken in all instances by the use of the tube. The purpose of this paper is to review the problem of bronchospasm seen during anesthesia in patients who, prior to anesthesia, did not have overt bronchospastic disease.

Bucking is a term commonly accepted by the anesthesiologists to describe a situation in which a patient is trying to cough and is straining on an endotracheal tube.

Bronchospasm is spasm of the bronchial musculature. Smooth muscle extends as far as the septums in the alveolar sacs, and so does spasm. Even an ordinary cough involves the smooth muscle as far as the finest bronchioles. Smooth muscle at this level is scanty, but in relation to their size the bronchioles are the most heavily muscled parts of the bronchial tree. Muscle spasm can close the bronchioles completely, since the muscle fibers located under the bronchial tunic propria are so oriented as to reduce the bronchiolar lumen and length when the muscle contracts.

In our experience, prolonged expiration is an early sign of bronchospasm. Phelps and Burdick[2] described the other classic signs: progressively increasing expiratory effort, expiratory wheeze, inspiratory effort, and cyanosis. The dangers of bronchospasm are anoxia, hypercapnia, pulmonary edema in a patient with a normal heart, precipitation of failure in a patient with a border-line myocardium, and postoperative atelectasis.[3]

Causes of Bronchospasm During Anesthesia

Bucking on Endotracheal Tube.—In bucking the patient is trying to cough, but he cannot close his glottis.[4] However, he can use the full musculature of the bronchial tree, down to the finest bronchioles. If the spasm persists, the result is a full-blown bronchospasm. Bucking may be evoked by an endotracheal tube by (1) intubating while the patient is in a plane of anesthesia which is too light, (2) permitting the intubated patient to reach too light a plane of anesthesia, (3) failing to obtain an adequate local anesthetic state in the endolarynx of the patient in a light plane of anesthesia, (4) giving a lightly anesthetized patient inadequate or ill-timed doses of muscle relaxants, (5) moving the tube or the patient's head, (6) inflating or deflating the cuff, (7) suctioning the tracheobronchial tree, or (8) manipulating the hilus in open chest surgery.

Irrespective of the cause, bucking is always an accompaniment of bronchospasm, which may persist after the bucking stops. While bucking persists it is difficult to get the agent into the lungs without forcing it, and forcing a potent agent into a hypoxic patient may depress the myocardium or even precipitate cardiac arrest.

Prevention of bucking is undoubtedly the best course. This usually can be accomplished by adequate topical anesthesia, sufficient depth of anesthesia, or adequate use of muscle relaxants. To obtain topical anesthesia, Bonica[5] advocates the transtracheal route, Severinghaus and De Backer[6] prefer the spray route, and we recommend, in addition to either of these methods, the use of the spray tube,[1] which permits reapplication of local anesthetics during the course of the anesthesia.

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The treatment of bucking should be determined by the cause. The cause must be ascertained and controlled to stop the bucking and prevent its recurrence.

Other Mechanical Causes of Bronchospasm.—Other causes of bronchospasm include stimulation of some part of the upper tracheobronchial tree by mucus, blood, or other foreign material.

Reflexes Which Tend to Evoke Bronchospasm.—Reflexes which tend to cause bronchospasm include the oculovagal, the nasovagal,[7] the hilar, the rib periosteum, the abdominal, and the pelvic. We have found that the pelvic reflexes, including those having their origin in the rectum, vagina, and cervix, tend to cause laryngospasm and cardiovascular effects rather than bronchospasm. Direct stimulation of the supracardiac thoracic vagus can precipitate severe bronchospasm as well as severe cardiac slowing.

The nasovagal reflex, although of importance in the cases of some asthmatics, has not been a clinical problem in patients under anesthesia. The oculovagal reflex, especially when manipulation of the medial rectus is the trigger for the reflex, usually has caused, in our experience, cardiac slowing, not bronchospasm. However, should the oculovagal reflex be found to evoke bronchospasm, the first treatment of the spasm would consist in stopping the stimulus. To prevent its recurrence, intravenously given atropine, found by Bosomworth and associates[8] to be effective, against cardiac slowing, might be equally useful against spasm of the bronchi. We have found that traction reflexes originating in the mesentery tend more often to depress heart rate and blood pressure than to evoke bronchospasm.

Errors in Technique.—Errors in technique in the conduct of anesthesia can also precipitate bronchospasm. For example, ether, although a bronchial dilator according to Adriani and Rovenstine,[9] can produce severe bronchial constriction if excessively high concentrations are administered. Conversely, cyclopropane, although known to be a bronchial constrictor, if well handled will not evoke spasm. The commonest error in the use of cyclopropane is the use of excessively high concentrations of this gas during induction. If spasm does develop, increasing the gas concentration with the intent to deepen the plane of anesthesia will augment the spasm by directly affecting the bronchial musculature.[9] The proper treatment of bronchospasm with cyclopropane is the dilution of the gas mixture with oxygen.[10] Dilution will reverse the process rapidly if the spasm is the consequence of high gas concentration. Deepening of anesthesia is indicated if the patient is intubated and is too lightly anesthetized to tolerate the tube. Forcing an irritating concentration of inhalation agent into an apneic patient after a barbiturate induction may cause spasm. This is especially true when an endotracheal tube is in place and the patient cannot close his glottis to exclude the agent.

Anesthetic Agents Which Can Evoke Spasm.—Several agents, drugs, and chemicals can evoke spasm of the bronchial musculature. Adriani and Rovenstine[9] found that pentothal, pentobarbital, evipal and phenobarbital, and morphine, as well as cyclopropane, produced narrowing of the bronchiolar lumen by direct contact. Ether, aside from its direct irritant action on the bronchial tree in high concentrations, evokes bronchorrhea, which can cause spasm. The muscarinic drug, physostigmine, is described by Macklin[11] as a source of bronchospasm. Edrophonium (Tensilon) chloride, a drug being used to treat curare overdosage, displays a similar muscarinic effect on bronchial musculature. We have seen two patients with border-line bronchial pathology who were made severely bronchospastic by edrophonium. The histamine-releasing effect of curare is said by Goodman and Gilman[12] to be more of a problem in dogs than in human beings. However, we have seen one patient in whom bronchospasm was precipitated by tubocurarine chloride, and he was successfully treated with intravenously given diphenhydramine (Benadryl) hydrochloride.

Chemical Irritants.—Two chemical irritants must be considered. Soda lime dust from poorly packed canisters, used in the to-and-fro method, is capable of producing bronchospasm. Gastric contents containing hydrochloric acid, even in minute amounts, once past the cords, go without hindrance to the farthest portions of the lung and evoke serious and persistent spasm of the entire bronchial tree.

Hypercapnia is, according to Peters,[13] capable of producing bronchospasm. He states that a pCO_2 of 56 to 84 mm. of mercury produced this reaction in dogs. We feel that this is not a problem in human beings at these or at even higher levels of pCO_2. Daly and his co-workers,[14] again using dogs, found that mixtures with low concentrations of O_2 to high concentrations of CO_2 were even more spasmogenic than mixtures with high concentrations of CO_2 alone. Again, we have not seen this reaction in human beings. In fact, considering the sympathetic discharge evoked by asphyxia, bronchospasm in human beings under these circumstances would seem unlikely to occur.

Prevention and Treatment of Bronchospasm

Means of prevention of spasm of the bronchial musculature include (1) adequate drying agent in the immediate preanesthetic period, (2) adequate depth of anesthesia at all times to obtund spasmogenic reflexes, (3) adequate local anesthesia during intubation (discussed as a means of prevention and treatment of bucking and of primary importance when patients are under very light anesthesia), counteract cardiac slowing, and it may be applicable to the prevention of bronchospasm. One of us (R. H. S.) has seen a 2% lidocaine solution applied topically to the area around the hilus to prevent a recurrence of bradycardia and bronchospasm produced by manipulation of the hilus. The patient with a history and signs suggesting borderline bronchial pathology merits special attention. Clearing low-grade chronic infections which produce sputum may be worthwhile since these patients seem prone to bronchospasm. The smoker who raises sputum after his first smoke of the day may do better under anesthesia if he has had his smoke and cleared his bronchi of the night's accumulation.

In the treatment of bronchospasm which has developed despite all efforts to prevent it, the following points may be kept in mind. Changing from a spasmogenic agent, such as cyclopropane, to a neutral one, such as nitrous oxide, may be effective. If *d*-tubocurarine chloride has been used, intravenously given antihistaminics may be helpful. If there is no contraindication, succinylcholine may be used. Recent work [17] and observations lead us to believe that a reevaluation of the effect of succinylcholine on human bronchial musculature is indicated. The drug appears to be highly effective in the treatment of bronchospasm. In any event, the use of this agent permits a thorough tracheobronchial toilet, which may be helpful. If gastric acid is aspirated, normal saline instilled into the pulmonary tree will dilute the hydrochloric acid and get it into solution for recovery by suctioning. One may be forced to conclude that the patient is a borderline asthmatic or bronchitic and resort to giving intravenously drugs such as aminophylline.

If the probability exists that the patient has sustained a pulmonary embolus, the treatment advocated by Jesser and DeTakáts [18] may be begun. This treatment comprises heavy dosages of atropine followed by papaverine. The hypothesis these investigators advance is that the bronchospasm attending pulmonary embolism is the lethal component and requires very rapid treatment. Finally, if protracted bronchospasm has resulted in cardiac failure symptoms with pulmonary edema, this must be treated quickly and efficiently.

Summary

The last full examination of the phenomenon called bronchospasm was made by Macklin in 1929. We have tried to supplement his findings and stress the problems of bronchospasm as related to anesthesia. The following points are of practical value in the prevention and treatment of bronchospasm.

Bucking invariably has a bronchospastic component which extends to the finest bronchioles. If bucking is allowed to persist, spasm may become a persisting problem. The spray tube prevents bucking in most cases and permits obtaining of a local reanesthetization of the larynx, trachea, and carina. When cyclopropane is involved in the genesis of bronchospasm, the proper treatment is withdrawal, not deepening. Edrophonium (Tensilon) chloride is a drug with a definite muscarinic effect on the bronchial musculature. It should be used with caution in the patient who has any degree of bronchial pathology which might tend toward irritability of the musculature. Succinylcholine appears to us to have an effect on bronchospasm which cannot be explained entirely by the chest wall relaxation. We feel that the effect is partly, at least, on the bronchial musculature.

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AMPHETAMINE, SECOBARBITAL, AND ATHLETIC PERFORMANCE

II. SUBJECTIVE EVALUATIONS OF PERFORMANCES, MOOD STATES, AND PHYSICAL STATES

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Amphetamine and secobarbital were compared with a placebo as to their effects on 57 college athletes. Performance was measured objectively. Subjective estimates of performance and mood were also obtained. Performance was significantly improved by 14 mg. of amphetamine sulfate, significantly impaired by 100 mg. of secobarbital, and not significantly influenced by 50 mg. of secobarbital. Subjects reported that amphetamine stimulated them, improved coordination and form, increased strength and endurance, and increased feelings of mental and physical activation, boldness, elation, and friendliness. The 100-mg. dose of secobarbital produced intoxication, elation, "deactivation," and distortion in judgment; the 50-mg. dose produced elation and activation.

An earlier paper [1] presented data showing that, in comparison with placebo, amphetamine sulfate, 14 mg., improved the performance of athletes; secobarbital sodium, 100 mg., impaired it; and secobarbital sodium, 50 mg., neither improved nor impaired athletic performance. The present paper deals with the subjective responses given by these same subjects (swimmers, runners, and weight-throwers) before and after they performed their athletic events. It presents quantitative data dealing with the drug effects reported by the athletes concerning specific aspects of performance, mood, and physical states.

Method

The earlier paper concerning objective performance[1] gave detailed descriptions of the characteristics of the experiments carried out with athletes. Table 1 summarizes the number and type of subjects used in each experiment, the number and types of medicaments used, the time intervals between medication and performance, and other methodological details essential to an understanding of the subjective data reported below.

Subjects.—Eighteen swimmers were studied 453 times, 26 runners gave 205 performances, and 13 weight-throwers gave 123 performances. All subjects except nine runners were members of college varsity or freshman teams. These nine were marathon runners, most of whom were beyond college age. All of these athletes were highly trained and in middle or late season condition. Six separate experiments were carried out with these 57 subjects (see table 1).

Medication Procedures.—All subjects in all experiments took placebos. In addition, those in experiment 1 took amphetamine sulfate (14 mg.) and secobarbital sodium (100 mg.) on different occasions; those in experiments 2, 3, and 5 took 14 mg. of amphetamine but 50 mg. of secobarbital. The subjects in experiment 4 took 50 mg. of secobarbital and took amphetamine in three different dosages (7, 14, and 21 mg.); the results obtained with the three dose levels of amphetamine are combined in the present paper. The subjects of the sixth experiment took 14 mg. of amphetamine but no seco-

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barbital. The medicaments were given on a body weight basis, the doses just mentioned being those given to a subject who weighed 70 kg. (154 lb.).

All medicaments were taken orally. Most subjects took each type several times (three on the average). In each study the drugs were given in a counterbalanced order which was unknown to the investigator collecting the data and unknown to the subjects. The athletes were told this was a study of the effect of "pep pills" on performance and that they would sometimes get blank pills instead of "pep pills." Secobarbital was not mentioned.

Preliminary studies (unpublished) indicated that the peak subjective effects of amphetamine occurred between two and four hours after administration, whereas those for secobarbital occurred between 30 minutes and two hours after administration. To obtain data during the period of maximum effect of each drug it was necessary, in the five experiments in which both active drugs were used, for the subjects to take two capsules each day. When a subject was scheduled to get secobarbital, his first capsule was a placebo; when he was scheduled to get amphetamine, the second was a placebo. Both capsules were placebos on placebo days. Table 1 shows the intervals maintained between the taking of active medicaments and the beginning of performance in each experiment.

TABLE 1.—*Summary of Methods Used in Studying the Effects of Amphetamine Sulfate and Secobarbital Sodium on Athletes*[*]

Experiment No.	No. of Subjects	Type of Subject[†]	Number of Sessions Scheduled for Each Type of Medication[‡]			Dosage, Mg. per 70 Kg. of Body Weight		Minutes Between Medication and Performance	
			P	A	S	A	S	A	S
1	15	Swimmer	4	4	4	14	100	120 & 180	55
2	8	Medium distance runner	3	3	3	14	50	120	60
3	8	Medium distance runner	2	2	2	14	50	120	60
4	9	Marathon runner	3	6	3	(7, 14, & 21)	50	120	15
5	13	Weight-thrower	4	4	4	14	50	120	60
6[§]	15	Swimmer	3	3	0	14	..	120	..

[*] P = placebo; A = amphetamine sulfate; S = secobarbital sodium.

[†] The subjects in experiment 1 swam once each day under rested and once under fatigued conditions. The subjects in all other experiments performed only once each day, under rested conditions. Medium distance runners means, in this report, men who ran between 440 yd. and 1 mile. Marathon runners ran between 4.5 and 12.7 miles. There were nine subjects in experiment 2, but the subjective data of one were discarded because he completed only three of the nine scheduled sessions. The medium distance runners of experiment 3 ran outdoors during winter; those in experiment 2 ran indoors. The marathon runners also ran outdoors during winter. The marathon runners ranged in age from 22 to 41 years; the subjects in all other experiments were between 18 and 24 years of age. Nine weight-throwers threw the 35-lb. weight and four put the 16-lb. shot.

[‡] Not all subjects completed all scheduled sessions; details concerning this are given in the earlier paper.[1]

[§] Sixteen subjects participated in experiment 6, but the subjective data of one subject were discarded because he completed only three sessions. Twelve of the subjects in experiment 6 were also used in experiment 1. The subjects in experiment 6 swam under conditions of high motivation, as described in the earlier paper.[1]

Data Collected.—Once before taking each medicament, and twice afterward, each subject indicated his mood and physical states by responding to an 81-item check list. The subject checked each of the 81 items, in relation to his then present state, as either not applying, slightly applying, or definitely applying.[2]

In addition, after completing each performance, the subject responded to a questionnaire containing 15 to 20 questions which were designed to help him evaluate his performance in a detailed way. Most of these questions were constructed in such a way as to have the subject indicate whether, with respect to a particular characteristic, his performance on any given day was better than usual, usual, or worse than usual. In all experiments two of the questions were: Do you think the effects of the drug helped or hurt your performance today and if so, how much and in what ways? Do you think these effects would help or hurt you in actual competition and if so, how? These two questions will be referred to as "general questions." The remaining questions, which dealt with more specific aspects of performance, will be termed "detail questions." The questionnaire used by the runners is reproduced below. The questionnaires used by the swimmers and weight-throwers were similar in general nature and intent but different in specific content.

Please check each of the following items to indicate whether it applies more or less than is usual for you. Use the center box if you do not differ from your usual state on that item.

1. Was this effort: an all-out one? [ ] less than all-out? [ ]
2. Was this run: easier? [ ] usual? [ ] harder? [ ]
3. Before the run were you "revved up" and eager to run all-out: more? [ ] usual? [ ] less? [ ]
4. Did your legs feel: strong? [ ] usual? [ ] weak? [ ]
5. Was this: paced, controlled effort? [ ] usual? [ ] just run, almost automatically? [ ]
6. Did you feel you were going: faster? [ ] usual? [ ] slower? [ ]
7. Did your running feel: tight? [ ] usual? [ ] loose? [ ]
8. Did your running feel: ragged and fighting? [ ] usual? [ ] smooth and rhythmic? [ ]
9. Was your tiredness point: earlier? [ ] usual? [ ] later? [ ]
10. Was your body responsive to your will: better? [ ] usual? [ ] worse? [ ]
11. After getting tired were you able to drive yourself: better? [ ] usual? [ ] worse? [ ]
    If either better or worse, please give details:
12. Was your form: better than usual? [ ] usual? [ ] worse than usual? [ ]
    If better or worse, please explain:
13. Was your recovery: faster? [ ] usual? [ ] slower? [ ]
    If faster or slower, please explain:
14. Do you have any pains: yes? [ ] no? [ ] Is this usual? yes? [ ] no? [ ]
    Please explain, telling where and when:

15. Do you believe there were any effects produced by the medication that either helped or hurt your performance: yes? [ ] no? [ ]
    How much and in what ways:
16. Do you think these effects would help or hurt you in actual competition use: yes? [ ] no? [ ]
    How much and in what ways:
17. Can you think of anything you have not already mentioned (things you noticed either before, during, or after running) which might help us learn about the effect the medication you had today has on athletic performance:

Treatment of Data.—The same general methods of scoring and statistical evaluation were used with all the data reported in this paper. The data in table 6 (obtained with the check list dealing with mood and physical states) will be used to exemplify and describe these methods. A subject was given a score of one on an item on the check list if he checked it as not applying, a score of two if he checked it as slightly applying, and a score of three if he checked it as definitely applying. Since most subjects received each medicament several times, each subject's mean score for each item was computed for each drug condition. Each comparison reported in table 6 indicates the number of subjects in a given experiment having higher mean scores on a given item on amphetamine days than on placebo days, the number having equal mean scores under the two "drug" conditions and the number having higher mean scores on placebo than on amphetamine days. Each probability value indicates the significance of the difference between the number of subjects having higher mean scores on amphetamine than on placebo days and the number having higher mean scores on placebo than on amphetamine days. If the number of subjects with higher amphetamine scores on a given item is significantly greater than the number with higher placebo scores on that item, it is stated that the group checked that item more on amphetamine than on placebo days; if the number of subjects with higher amphetamine scores is significantly lower than the number with higher placebo scores, it is stated that the group checked the item less on amphetamine than on placebo days. Comparisons failing to reach the 0.10 level of significance, with a two-tailed test, are called nonsignificant in this paper; those reaching the 0.10, 0.05, or 0.01 levels are said to be significant. The level of significance is specified in each case in the tables. The statistical test used to evaluate the comparisons just referred to is the binomial sign test.[3] The sign test is much faster than the t test, although less sensitive. Since the subjective comparisons were numerous, the speed afforded by the sign test was advantageous.

TABLE 2.—*Subjective Evaluations of Effects of Amphetamine, Placebo, and Secobarbital on Athletic Performance*[*]

	Group of Athletes	A>P	A=P	P>A	p	S>P	S=P	S=P	p
Do you think the medication you had today helped or hurt your performance? If so, how much and in what ways?	Weight-throwers (n=13)	9	3	1	0.05	7	5	1	0.10
	Runners (n=16), medium distance	6	10	0	0.05	4	11	1	NS
	Runners (n=9), marathon distance	5	4	0	0.10	1	7	1	NS
	Swimmers (n=15), experiment 1	(9)	(2)	(4)	(NS)	(6)	(5)	(4)	(NS)
	Swimmers (n=15), experiment 6	(10)	(3)	(2)	(0.05)	No data collected			
	Swimmers (n=18), both groups combined	13	2	3	0.05	*No combined analysis performed*			
	Total (A vs. P, n=56; S vs. P, n=38)	33	19	4	0.01	12	23	3	0.05
	%	59	34	7	...	32	60	8	
Do you think the medication you had today would help or hurt you in actual competition? If so, how much and in what ways?	Weight-throwers (n=13)	9	4	0	0.01	7	3	3	NS
	Runners (n=16), medium distance	4	11	1	NS	5	11	0	0.10
	Runners (n=9), marathon distance	5	4	0	0.10	3	5	1	NS
	Swimmers (n=15), experiment 1	(8)	(2)	(5)	(NS)	(5)	(3)	(7)	(NS)
	Swimmers (n=15), experiment 6	(10)	(3)	(2)	(0.05)	No data collected			
	Swimmers (n=18), both groups combined	10	5	3	0.10	No combined analysis performed			
	Total (A vs. P, n=56; S vs. P, n=38)	28	21	4	0.01	15	19	4	0.05
	%	50	43	7	...	39	50	11	...

[*] A=amphetamine sulfate; P=placebo; S=secobarbital sodium; see table 1 for dosages. A>P=number of subjects reporting more help from amphetamine than placebo. p=probability based on two-tailed binomial sign test of the difference between A>P and P>A or the difference between S>P and P>S. 12 swimmers participated in both swimming experiments; there were 18 different swimmers altogether. The swimmers of experiment 1 received a different dosage of secobarbital from that given the remaining subjects and therefore are not included in the total figures for the secobarbital-placebo comparisons. NS=not significant.

Results

The results are given in two parts. The first presents the performance evaluations reported by the athletes on amphetamine and secobarbital days in comparison with those reported on placebo days. The second presents results obtained with the 81-item check list and deals with the effects of amphetamine and secobarbital, in comparison with placebo, on subjective responses concerning mood and physical states. In examining the results reported in both sections it should be borne in mind that all groups of athletes actually performed better after taking amphetamine than after taking placebo, and that the performance of the swimmers was significantly impaired by 100 mg. of secobarbital, while the performance of runners and weight-throwers, considered as groups, was neither improved nor impaired, significantly, by 50 mg. of secobarbital.

Performance Evaluation of Athletes

Amphetamine and Two "General Questions."—Table 2 deals with the two "general questions" and reports comparisons for each experiment considered separately and for all experiments combined. The data reported in table 2 for the swimmers of experiment 1 are based on four different experimental conditions combined: swimming alone when rested, alone when fatigued, in groups of three when rested, and in groups when fatigued.

TABLE 3.—*Subjective Evaluations of Effects of Amphetamine, Placebo, and Secobarbital Reported by Fifteen Swimmers Under Four Experimental Conditions*

Do you think the medication you had today helped or hurt your performance? If so, how much and in what ways?	A>P	A=P	P>A	p	S>P	S=P	P>S	p
Rested, alone	9	4	2	0.10	8	5	2	NS
Rested, groups	6	5	4	NS	5	3	7	NS
Fatigued, alone	3	10	2	NS	7	6	2	NS
Fatigued, groups ..	3	8	4	NS	2	6	7	NS

Do you think the medication you had today would help or hurt you in actual competition? If so, how much and in what ways?	A>P	A=P	P>A	p	S>P	S=P	P>S	p
Rested, alone	6	9	0	0.05	6	7	2	NS
Rested, groups	5	5	5	NS	4	4	7	NS
Fatigued, alone	3	10	2	NS	5	7	3	NS
Fatigued, groups ..	3	8	4	NS	3	5	7	NS

Table 3 gives results concerning responses to the two "general questions," with a breakdown of the four experimental conditions. When the subjects from all experiments were combined into a single group, it was found that 33 subjects (59%) reported receiving more help on amphetamine than on placebo days, 19 subjects (34%) reported no difference, and 4 subjects (7%) reported receiving more help on placebo than on amphetamine days; 28 subjects (50%) reported amphetamine would be better than placebo for competition, 24 subjects (43%) reported no difference, and 4 subjects (7%) reported placebo would be better than amphetamine for competition. Concerning both questions the number of subjects favoring amphetamine was significantly greater ($p < 0.01$) than the number favoring placebo. The actual fact was that 77% of the subjects performed better after taking amphetamine than after placebo, and 23% performed worse.

Amphetamine and the "Detail Questions."—Table 4 presents the amphetamine-placebo comparisons based on the "detail questions" concerning performance. Eight "detail questions" showed significant differences in the answers of the 25 runners to the questionnaire on amphetamine and on placebo days. The runners reported that they felt more "revved up" before the race, their legs felt stronger, their running felt faster and easier, they tired later, their bodies responded better to their will, their running was more smooth and rhythmic, and their effort was less "all-out" on amphetamine than on placebo days. All of these items except the last definitely indicated that the subjects reported better effects on amphetamine than on placebo days (table 4).

The responses of the 13 weight-throwers yielded nine significant differences between amphetamine and placebo, all nine of which were in the direction of better performance on amphetamine than on placebo days (table 4). The weight-throwers reported better coordination, easier throwing, greater smoothness of motion, greater strength, greater endurance, throwing more "all-out," better balance and footwork, feet down more solidly after turns, and more snap and explosion at the release on amphetamine than on placebo days.

The reports of the 15 swimmers of experiment 6 yielded four significant differences between amphetamine and placebo, all in the direction of better performance on amphetamine days. They reported that they were more "revved up" before the race, swam faster, felt looser, and made their turns better on amphetamine than on placebo days. The effects shown by the 15 swimmers of experiment 1 were much less definite than those shown by the other groups and were not internally consistent (table 4).

TABLE 4.—*Comparative Effects of Amphetamine and Placebo on Subjective Evaluations of Performance*

Group of Athletes	Questionnaire Item*	A>P†	A=P	P>A	p
Runners (n=25)	"Revved up" before race..	17	6	2	0.01
	Legs felt strong..........	19	1	5	0.01
	Running felt fast.........	17	4	4	0.01
	Running seemed easy.....	17	4	4	0.01
	Good endurance..........	18	2	5	0.05
	Body responsive to will...	12	9	4	0.10
	Running with smoothness and rhythm.............	14	6	5	0.10
	Effort "all-out"..........	2	14	9	0.10
Weight-throwers (n=13)	Good coordination in throwing................	11	2	0	0.01
	Throwing with ease.......	12	0	1	0.01
	Smoothness of motion...	11	0	2	0.05
	Good strength............	11	0	2	0.05
	Good endurance..........	9	3	1	0.05
	Throwing "all-out".......	7	6	0	0.05
	Good balance and footwork	9	2	2	0.10
	Feet down solidly after turns‡....................	7	1	1	0.10
	Release with explosion or snap.....................	9	2	2	0.10
Swimmers (n=15), experiment 6	"Revved up" before race..	11	3	1	0.01
	Swimming felt fast.......	12	0	3	0.05
	Swimming felt loose......	9	5	1	0.05
	Made turns well...........	7	7	1	0.10
Swimmers (n=15), experiment 1					
First swim, swimming alone	"Revved up" before race..	9	4	2	0.10
First swim, swimming in groups	No significant effects......	...	...	...	...
Second swim, swimming alone	Recovery was fast........	0	7	8	0.01
Second swim, swimming in groups	Swimming felt easy.......	2	4	9	0.10
	Start was fast............	1	6	8	0.05

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* Only those items yielding a significant difference between A>P and P>A are listed in this table.

† On all items the number of athletes who reported more favorable effects on amphetamine than on placebo days is listed under A>P.

‡ This question did not apply to the four shot putters.

Secobarbital and the Two "General Questions."—Thirty-eight subjects (runners and weight-throwers) received 50 mg. of secobarbital. Table 2 shows that 12 of these 38 subjects (32%) reported receiving more help on secobarbital than on placebo days, 23 subjects (60%) reported no difference, and 3 subjects (8%) reported more help on placebo than on secobarbital days; 15 subjects (39%) reported that secobarbital would be better than placebo for competition, 19 subjects (50%) reported no difference, and 4 subjects (11%) reported placebo would be better than secobarbital for competition. Concerning both "general questions," the number of subjects favoring secobarbital was significantly greater ($p=0.05$) than the number favoring placebo. The actual fact was that 53% of the subjects performed better on secobarbital days than on placebo days, and 47% performed worse.

Table 3 shows that the 15 swimmers in experiment 1 who were given the 100-mg. dose of secobarbital did not yield significant secobarbital-placebo differences with respect to the two "general questions" under any of the four experimental conditions, although there was a tendency for the subjects to favor secobarbital when swimming alone and a tendency to favor placebo when swimming in groups. In actuality 93% of the subjects were impaired under the group-rested condition, 93% under the group-fatigued, 87% under the alone-rested, and 67% under the alone-fatigued condition.

Secobarbital and the "Detail Questions."—Although the runners and weight-throwers attributed more advantageous effects to 50 mg. of secobarbital than to placebo when asked the two "general questions," their responses to the "detail questions" on the performance-evaluation questionnaire failed to indicate any significant differences between secobarbital and placebo (table 5). This is in contrast to the many significant amphetamine-placebo differences found with the "detail questions" (table 4).

TABLE 5.—*Comparative Effects of Secobarbital and Placebo on Subjective Evaluations of Performance**

Groups of Athletes	Questionnaire Item	Swimming Alone				Swimming in Groups			
		S>P	S=P	P>S	p	S>P	S=P	P>S	p
Swimmers (n=15), experiment 1									
First swim, rested	Stroke felt good	11	4	0	0.01	9	3	3	NS
	Swimming felt loose	10	5	0	0.01	5	6	4	NS
	Start seemed fast	8	7	0	0.01	3	6	6	NS
	Recovery was fast	5	5	5	NS	10	4	1	0.05
	Swimming felt fast	10	3	2	0.05	9	1	5	NS
	Swimming felt smooth	10	3	2	0.05	7	4	4	NS
	Swimming seemed easy	9	5	1	0.05	10	1	4	NS
	Made turns well	8	6	1	0.05	6	4	5	NS
	Did not have to drive self hard toward finish	9	4	2	0.10	8	4	3	NS
Second swim, fatigued	Swimming felt smooth	8	7	0	0.01	6	3	6	NS
	Start seemed fast	9	5	1	0.05	4	8	3	NS
	Made turns well	9	5	1	0.05	5	6	4	NS
	Swimming felt fast	11	1	3	0.10	6	6	3	NS
Runners (n=25)									no significant effects
Weight-throwers (n=13)									no significant effects
Swimmers (n=15), experiment 6									secobarbital not given

* The dose of secobarbital sodium given to the swimmers of experiment 1 was 100 mg. per 70 kg. of body weight. That given to the runners and weight-throwers was 50 mg. per 70 kg. of body weight.

Table 5 shows that the answers to the "detail questions" given by the 15 swimmers who took the 100-mg. dose of secobarbital indicated that, when swimming alone, they definitely evaluated the effects of that medicament favorably; when swimming in groups, there was a tendency to attribute favorable effects to the drug, but only one comparison was statistically significant. The attribution of favorable effects to 100 mg. of secobarbital was in conflict with the fact, just mentioned, that secobarbital impaired the performance of the subjects under all four experimental conditions.

Mood and Physical States

Reported Effects of Amphetamine.—The results of the comparisons between the way the subjects checked the 81-item check list on amphetamine days and the way they checked it on placebo days are presented in table 6. The left-hand side of the table deals with responses obtained 10 to 30 minutes before beginning the performance (from one and one-half to two and one-half hours after administration) and the right-hand side deals with responses obtained 10 to 30 minutes after completing the performance (from two and one-half to three and one-half hours after administration).

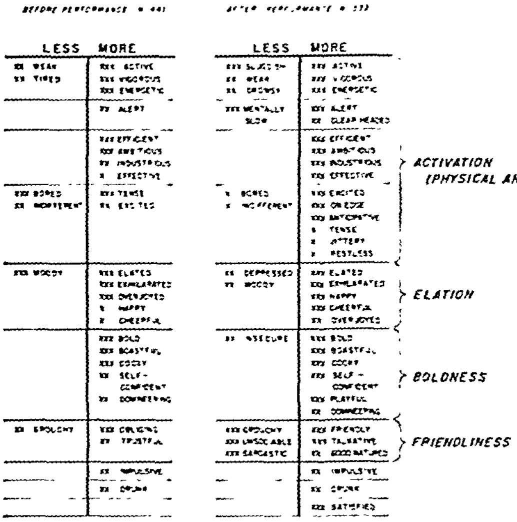
In addition to the data reported in tables 6 and 7 and in the figure, data were also collected concerning mood and physical states before each medicament was administered. This was done to determine whether chance sampling factors might be contributing bias to the drug comparisons. A bias of this sort was found in experiment 1 and will be discussed later.

The 729 comparisons in table 6 do not readily point up the major conclusions suggested by the data. The figure presents, in a manner facilitating quick comprehension, the effects of amphetamine on mood and physical states in experiments 2 through 6, combined. Twelve of the subjects in experiment 6 had also participated in experiment 1. To prevent those 12 subjects from contributing twice to the total comparisons (based on all subjects combined to form a single group), the decision was made to exclude one of these two experiments from the total comparisons. The mood and physical effects found in experiment 6 were like those found in experiments 2-5, but those found in experiment 1 were different. Possible reasons for this will be suggested. Because the results in experiment 6 received confirmation from those in experiments 2-5, whereas those of experiment 1 did not, the decision was made to include experiment 6 rather than experiment 1 in the overall total.

The figure summarizes the results based on the data of experiments 2 through 6, combined, and shows that the four major subjective states produced by amphetamine both before and after performance were (1) mental and physical activation, (2) elation, (3) boldness, and (4) friendliness. The "clustering" of items in the figure is based on what we believe to be psychological and semantic similarities. The significance levels are reported for each item separately, for the convenience of the reader who does not agree with this grouping.

The increased feeling of mental and physical activation was the most definite amphetamine effect revealed by responses to the 81-item check list, both before and after performance. At one or both points there was more checking of active, vigorous, and energetic on amphetamine than on placebo days; less checking of sluggish, weak, drowsy, and tired; more checking of alert and clearheaded; less checking of mentally slow; more checking of efficient, ambitious, industrious, and effective; and more checking of excited, on edge, anticipative, tense, jittery, and restless on amphetamine than on placebo days. The second most definite amphetamine effect revealed by responses to the check list was increased elation. There was more checking of elated, exhilarated, happy, cheerful, and overjoyed and less checking of depressed and moody on amphetamine days than on placebo days. A third positive effect was increased boldness. The subjects checked bold, boastful, cocky, self-confident, playful, and domineering more, and insecure less, on amphetamine than on placebo days. The fourth definite effect was greater friendliness, as indicated by more checking of friendly, talkative, good-natured, obliging, and trustful and less checking of grouchy, unsociable, and sarcastic. In addition to the four major effects just mentioned, there was also greater checking of impulsive and drunk on amphetamine than on placebo days, both before and after performance; and there was greater checking of satisfied after performance on amphetamine than on placebo days.

Reported Effects of Secobarbital on Mood and Physical States.—The 100-mg. dose of secobarbital was used in the first experiment only. The subjects checked the 81-item list 30 minutes after taking secobarbital (25 minutes before beginning the first swim) and again about 80 minutes after administration (after completing the second swim). The major effect at both time points was one of intoxication, as indicated by greater checking of dopey, light-headed, and drunk after secobarbital than after placebo (table 7). At the 30-minute point there was also more checking of dizzy and muddled and less checking of clear-headed on secobarbital than on placebo days. The remaining effects produced by 100 mg. of secobarbital were less definite than the intoxication, and those present before performance differed from those present afterward (table 7). Before performance there was a "deactivation" effect, as indicated by less checking of industrious and active on secobarbital than on placebo days; there was also less checking of good-natured, cautious, and hungry. After performance, there was an increase in elation, as indicated by more checking of cheerful, elated, and happy on secobarbital than on placebo days; there was also more checking of nonchalant and less checking of insecure, less checking of sarcastic, less checking of self-controlled, and more checking of industrious on secobarbital than on placebo days.



Effects of amphetamine on mood and physical states; xxx: significant at 0.01 level, by two-tailed binomial sign test; xx: significant at 0.05 level; x: significant at 0.10 level.

The 50-mg. dose of secobarbital given to runners and weight-throwers produced less definite effects on mood and physical states than did the 100 mg. dose given to swimmers (table 7). Before the performance there was more elation on secobarbital than on placebo days, as indicated by more checking of elated, overjoyed, and exhilarated; more mental and physical activation, surprisingly, as in-

TABLE 6.—*Subjective Evaluation of Effects*

	Amphetamine vs. Placebo, per Experiment No. (Before Performance)															
	1 (n = 15)				2 & 3 (n = 16)				5 (n = 13)				6 (n = 15)			
Item	+	=	−	p	+	=	−	p	+	=	−	p	+	=	−	p
Alert	3	7	5	...	6	6	4	...	6	4	3	...	8	7	0	0.01
Unsociable	1	11	3	...	3	9	4	...	3	9	1	...	3	9	3	...
Hungry	3	4	8	...	5	7	4	...	2	7	4	...	4	7	4	...
Dreamy	4	9	2	...	5	9	2	...	2	8	3	...	3	10	2	...
Talkative	8	3	4	...	7	4	5	...	4	6	3	...	5	9	1	...
Chilly	4	9	2	...	0	8	8	0.01	2	10	1	...	2	11	2	...
Bold	5	7	3	...	5	11	0	0.10	7	6	0	0.05	2	12	1	...
Sluggish	3	5	7	...	3	7	6	...	2	3	8	...	4	7	4	...
Friendly	5	7	3	...	3	9	4	...	3	6	4	...	9	5	1	0.05
Thirsty	5	3	7	...	2	11	3	...	5	5	3	...	4	7	4	...
On edge	6	5	4	..	2	8	6	...	5	7	1	...	5	6	4	...
Vigorous	5	7	3	...	10	6	0	0.01	10	2	1	0.05	9	5	1	0.05
Pensive	5	5	5	...	2	10	4	...	1	8	4	...	2	10	3	...
Drunk	1	13	1	...	0	15	1	...	6	7	0	0.05	3	12	0	...
Nonchalant	3	10	2	...	6	4	6	...	1	10	2	...	2	8	5	...
Efficient	5	7	3	...	8	7	1	0.05	5	7	1	...	7	7	1	0.10
Skeptical	3	10	2	...	2	8	6	...	2	7	4	...	2	9	4	...
Self-confident	8	5	2	...	6	7	3	...	7	4	2	...	7	5	3	...
Erotic	3	9	3	...	5	7	4	...	2	7	4	...	3	11	1	...
Good-natured	4	5	6	...	5	7	4	...	5	5	3	...	7	4	4	...
Mentally cloudy	2	8	5	...	5	7	4	...	1	9	3	...	5	5	5	...
Cheerful	8	4	3	...	5	9	2	...	5	6	2	...	7	5	3	...
Impatient	7	5	3	...	6	7	3	...	5	6	2	...	4	5	6	...
Energetic	6	7	2	...	7	8	1	0.10	8	3	2	...	7	6	2	...
Timid	0	15	0	...	2	11	3	...	1	9	3	...	1	13	1	...
Anticipative	5	6	4	...	5	8	3	...	4	5	4	...	9	4	2	0.10
Angry	2	10	3	...	2	12	2	...	3	8	2	...	1	11	3	...
Playful	6	7	2	...	8	4	4	...	4	6	3	...	5	9	1	...
Insecure	5	7	3	...	2	11	3	...	3	8	2	...	4	10	1	...
Bored	1	7	7	0.10	1	8	7	0.10	1	10	2	...	1	8	6	...
Dizzy	4	10	1	...	4	10	2	...	4	7	2	...	3	9	3	...
Indifferent	2	6	7	...	3	5	8	...	2	7	4	...	1	8	6	...
Shaky	3	11	1	...	0	9	7	0.05	5	6	2	...	2	11	2	...
Domineering	4	10	1	...	6	8	2	...	5	8	0	0.10	1	13	1	...
Active	5	6	4	...	10	4	2	0.05	8	3	2	....	7	5	3	...
Blurry-eyed	2	10	3	...	1	10	5	...	3	8	2	...	2	10	3	...
Peaceful	4	5	6	...	9	4	3	...	3	4	6	...	6	7	2	...
Industrious	5	6	4	...	8	5	3	...	5	5	3	...	7	7	1	0.10
Depressed	7	2	6	...	1	11	4	...	3	6	4	...	5	2	8	...
Effective	6	5	4	...	6	7	3	...	6	5	2	...	7	5	3	...
Cautious	0	7	8	0.01	4	7	5	...	1	7	5	...	2	8	5	...
Drowsy	2	6	7	...	6	5	5	...	2	8	3	...	3	4	8	...
Sarcastic	4	5	6	...	4	8	4	...	1	9	3	...	3	10	2	...
Ambitious	4	8	3	...	11	5	0	0.01	9	3	1	0.05	5	8	2	...
Inhibited	3	10	2	...	2	10	4	...	4	8	1	...	3	10	2	...
Changeable	6	6	3	...	3	8	5	...	3	7	3	...	4	8	3	...
Tense	4	6	5	...	5	8	3	...	7	5	1	0.10	5	4	6	...
Jittery	2	9	4	...	1	12	3	...	5	7	1	...	2	7	6	...
Quiet	0	8	7	0.05	6	6	4	...	1	6	6	...	3	8	4	...
Unworried	5	3	7	...	4	5	7	...	3	5	5	...	6	4	5	...
Numb	3	11	1	...	3	9	4	...	3	9	1	...	2	10	3	...
Sad	4	9	2	...	0	13	3	...	2	10	1	...	4	7	4	...
Restless	5	5	5	...	5	4	7	...	8	4	1	0.05	6	4	5	...
Trustful	3	10	2	...	5	9	2	...	4	9	0	...	4	10	1	...
Dopey	3	6	6	...	3	9	4	...	4	6	3	...	4	10	1	...
Boastful	3	12	0	...	4	11	1	...	6	6	1	...	4	11	0	...
Happy	8	5	2	...	6	7	3	...	6	4	3	...	7	5	3	...
Relaxed	3	8	4	...	6	7	3	...	1	7	5	...	4	8	3	...
Headache	3	10	2	...	4	9	3	...	1	8	4	...	2	9	4	...
Cocky	2	13	0	...	6	9	1	...	6	6	1	...	4	10	1	...
Blue	4	7	4	...	1	12	3	...	2	8	3	...	1	9	5	...
Weak	3	4	8	...	2	5	9	0.10	3	3	7	...	4	4	7	...
Excited	3	7	5	...	6	6	4	...	6	5	2	...	6	8	1	...
Moody	3	8	4	...	0	8	8	0.01	3	7	3	...	1	6	8	0.05
Satisfied	5	5	5	...	4	6	6	...	3	5	5	...	6	7	2	...
Impulsive	7	5	3	...	4	10	2	...	5	7	1	...	7	7	1	0.10
Tired	2	5	8	...	3	6	7	...	3	4	6	...	3	4	8	...
Detached	6	6	3	...	3	10	3	...	3	9	1	...	3	8	4	...
Defiant	5	8	2	...	3	10	3	...	3	9	1	...	2	8	5	...
Self-conscious	4	8	3	...	2	9	5	...	3	8	2	...	2	10	3	...
Lightheaded	6	7	2	...	4	9	3	...	6	6	1	...	5	7	3	...
Grouchy	3	8	4	...	2	10	4	...	2	8	3	...	0	8	7	0.05
Elated	6	8	1	...	6	10	0	0.05	5	8	0	0.10	8	7	0	0.01
Clearheaded	7	5	3	...	7	7	2	...	3	7	3	...	8	6	1	0.05
Obliging	5	5	5	...	6	10	0	0.05	5	6	2	...	4	10	1	...
Overjoyed	3	11	1	...	6	9	1	...	6	7	0	0.05	2	13	0	...
Mentally slow	2	9	4	...	1	10	5	...	2	7	4	...	4	8	3	...
Self-controlled	4	6	5	...	4	9	3	...	4	6	3	...	4	9	2	...
Frustrated	6	7	2	...	4	10	2	...	2	8	3	...	2	5	8	...
Muddled	6	6	3	...	3	9	4	...	5	6	2	...	1	10	4	...
Exhilarated	5	8	2	...	7	8	1	0.10	7	5	1	0.10	3	12	0	...

See table 1 for a tabulation of methodological factors in the six experiments.

* The number of subjects checking a given item more on amphetamine days than on placebo days is listed in the + column. The = column re-
placebo than on amphetamine days. p. indicates the two-tailed probability value based on the binomial sign test evaluation of the difference between
nificance are left blank.

*of Amphetamine—Tabulation of Responses**

Amphetamine vs. Placebo, per Experiment No. (After Performance)																			
1 (n = 15)				2 & 3 (n = 16)				4† (n = 9)				5 (n = 13)				6 (n = 15)			
+	=	—	p	+	=	—	p	+	=	—	p	+	=	—	p	+	=	—	p
4	5	6	...	10	5	1	0.05	3	5	1	...	9	4	0	0.01	10	2	3	0.10
3	12	0	...	1	10	5	...	1	6	2	...	0	7	6	0.05	1	11	3	...
1	7	7	0.10	3	9	4	...	0	4	5	0.10	2	7	4	...	7	6	2	...
2	12	1	...	4	7	5	...	1	5	3	...	0	10	3	...	6	8	1	...
3	7	5	...	5	8	3	...	5	3	1	...	9	4	0	0.01	6	5	4	...
2	11	2	...	2	10	4	...	4	2	3	...	2	9	2	...	4	9	2	...
2	10	3	...	7	8	1	0.10	3	6	0	...	6	6	1	...	4	10	1	...
5	6	4	...	3	7	6	...	1	5	3	...	0	4	9	0.01	4	1	10	...
2	8	5	...	7	8	1	0.10	4	2	3	...	9	3	1	0.05	5	9	1	...
3	5	7	...	2	7	7	...	5	2	2	...	6	5	2	...	5	6	4	...
2	8	5	...	4	9	3	...	3	6	0	...	8	5	0	0.01	5	7	3	...
2	7	6	...	6	8	2	...	8	0	1	0.05	10	3	0	0.01	5	7	3	...
2	10	3	...	5	9	2	...	3	5	1	...	0	9	4	...	2	12	1	...
1	13	1	...	2	13	1	...	1	8	0	...	4	9	0	...	2	13	0	...
3	8	4	...	4	6	6	...	2	4	3	...	0	8	5	0.10	3	10	2	...
2	9	4	...	6	9	1	...	3	3	3	...	7	5	1	0.10	6	7	2	...
1	8	6	...	3	13	0	...	2	5	2	...	1	7	5	...	2	9	4	...
3	5	7	...	6	9	1	...	5	1	3	...	8	3	2	...	8	6	1	0.05
3	9	3	...	3	9	4	...	1	6	2	...	1	8	4	...	0	14	1	...
6	6	3	...	6	7	3	...	3	3	3	...	7	6	0	0.05	7	5	3	...
5	5	5	...	3	10	3	...	1	6	2	...	2	8	3	...	2	4	9	0.10
4	6	5	...	6	8	2	...	5	4	0	0.10	8	5	0	0.01	7	6	2	...
3	6	6	...	6	9	1	...	4	3	2	...	4	6	3	...	3	7	5	...
4	6	5	...	7	5	4	...	6	0	3	...	12	1	0	0.01	7	7	1	0.10
3	10	2	...	2	10	4	...	0	9	0	...	1	8	4	...	1	12	2	...
2	9	4	...	9	6	1	0.05	4	4	1	...	3	8	2	...	5	8	2	...
2	9	4	...	2	13	1	...	2	6	1	...	2	8	3	...	2	6	7	...
1	12	2	...	6	9	1	...	5	3	1	...	7	5	1	0.10	6	6	3	...
3	8	4	...	2	10	4	...	0	5	4	...	1	10	2	...	1	9	5	...
0	9	6	0.05	3	10	3	...	1	6	2	...	0	9	4	...	1	10	4	...
7	7	1	0.10	2	8	6	...	1	7	1	...	2	9	2	...	5	6	4	...
4	6	5	...	3	9	4	...	2	3	4	...	1	5	7	0.10	2	9	4	...
5	8	2	...	3	5	8	...	1	7	1	...	6	7	0	0.05	4	7	4	...
2	10	3	...	4	11	1	...	4	5	0	...	3	10	0	...	1	12	2	...
3	6	6	...	8	7	1	0.05	7	2	0	0.05	11	1	1	0.01	8	5	2	...
4	8	3	...	3	8	5	...	3	6	0	...	2	8	3	...	5	9	1	...
2	4	9	0.10	4	8	4	...	3	4	2	...	6	4	3	...	4	6	5	...
3	6	6	...	6	6	4	...	5	2	2	...	8	3	2	...	6	7	2	...
3	4	8	...	4	8	4	...	1	5	3	...	1	4	8	0.05	2	5	8	...
1	9	5	...	6	9	1	...	6	2	1	...	10	3	0	0.01	7	7	1	0.10
3	9	3	...	4	8	4	..	1	5	3	...	1	10	2	...	2	10	3	...
3	4	8	...	1	8	7	0.10	1	6	2	...	1	6	6	...	5	4	6	...
2	7	6	...	1	9	6	...	0	7	2	...	1	9	3	...	2	7	6	...
4	3	8	...	6	9	1	...	7	0	2	...	9	2	2	0.10	6	8	1	...
3	10	2	...	5	9	2	...	1	6	2	...	4	6	3	...	0	12	3	...
5	7	3	...	3	6	7	...	3	6	0	...	1	8	4	...	4	9	2	...
7	4	4	...	4	9	3	...	1	7	1	...	6	6	1	...	5	7	3	...
6	4	5	...	2	10	4	...	1	7	1	...	7	6	0	0.05	6	8	1	...
6	5	4	...	6	7	3	...	1	2	6	...	2	4	7	...	3	7	5	...
1	7	7	0.10	4	7	5	...	3	4	2	...	5	7	1	...	6	5	4	...
7	4	4	...	5	6	5	...	2	7	0	...	2	9	2	...	7	3	5	...
1	11	3	...	3	9	4	...	1	7	1	...	0	9	4	...	2	9	4	...
1	7	7	0.10	6	7	3	...	5	4	0	0.10	7	6	0	0.05	3	5	7	...
1	11	3	...	4	10	2	...	3	4	2	...	2	9	2	...	3	11	1	...
5	8	2	...	1	10	5	...	1	7	1	...	2	9	2	...	5	8	2	...
2	11	2	...	5	9	2	...	4	5	0	...	5	8	0	0.10	3	11	1	...
4	7	4	...	6	9	1	...	6	2	1	...	8	3	2	...	9	4	2	0.10
2	6	7	...	8	5	3	...	4	1	4	...	4	3	6	...	7	3	5	...
9	4	2	0.10	1	11	4	...	1	7	1	...	0	10	3	...	5	5	5	...
1	13	1	...	5	10	1	...	4	5	0	...	4	8	1	...	2	12	1	...
4	6	5	...	4	9	3	...	1	5	3	...	0	8	5	0.10	2	10	3	...
7	5	3	...	3	5	8	...	2	3	4	...	3	2	8	...	4	4	7	...
3	8	4	...	4	11	1	...	5	4	0	0.10	7	6	0	0.05	5	9	1	...
3	6	6	...	1	7	8	0.05	1	7	1	...	0	7	6	0.05	4	9	2	...
5	5	5	...	6	6	4	...	7	1	1	0.10	9	2	2	0.10	9	2	4	...
1	11	3	...	2	12	2	...	2	7	0	...	5	7	1	...	7	6	2	...
7	4	4	...	4	5	7	...	2	2	5	...	2	3	8	...	5	4	6	...
4	4	7	...	2	12	2	...	1	7	1	...	3	6	4	...	3	6	6	...
1	6	8	0.05	3	9	4	...	3	5	1	...	3	8	2	...	4	5	6	...
2	10	3	...	4	10	2	...	1	5	3	...	0	10	3	...	1	9	5	...
5	7	3	...	1	11	4	...	3	5	1	...	5	7	1	...	4	8	3	...
5	5	5	...	1	9	6	...	1	6	2	...	0	7	6	0.05	2	7	6	...
2	10	3	...	4	11	1	...	6	2	1	...	6	5	2	...	4	9	2	...
3	6	6	...	7	7	2	...	2	5	2	...	7	6	0	0.05	7	5	3	...
6	4	5	...	5	8	3	...	2	5	2	...	4	7	2	...	5	9	1	...
4	9	2	...	3	12	1	...	4	5	0	...	4	9	0	...	0	14	1	...
5	5	5	...	3	8	5	...	0	6	3	...	0	6	7	0.05	3	3	9	...
3	7	5	...	4	10	2	...	3	4	2	...	3	9	1	...	5	8	2	...
8	5	2	...	4	8	4	...	3	4	2	...	1	8	4	...	3	8	4	...
5	8	2	...	3	10	3	...	4	5	0	...	1	8	4	...	2	7	6	...
1	13	1	...	4	11	1	...	5	3	1	...	6	7	0	0.05	4	10	1	...

ports the number of subjects checking items equally under the two drugs and the — column lists the number of subjects checking items more on the number of subjects listed under the + column and the number listed under the — column. All comparisons failing to reach the 0.10 level of sig-

† The subjects of experiment 4 did not complete the check list before performance.

dicated by more checking of vigorous, efficient, and ambitious, and less checking of weak; and, in addition, a suggestion of intoxication, as indicated by more checking of light-headed on secobarbital than on placebo days. The effects of 50 mg. of secobarbital, found after the performance, did not fall into coherent groups and tended to differ from experiment to experiment (table 7).

Comment

The data presented above, dealing with the drug effects reported by the athletes concerning performance, mood, and physical states, shed light on several specific questions which in some cases are not closely related to each other. In discussing the results, each of these questions will be treated separately.

TABLE 7.—*Subjective Evaluation of Effects*

Item	Secobarbital vs. Placebo, per Experiment No. (Before Performance)															
	1 (n = 15)				2 & 3 (n = 16)				5 (n = 13)				2, 3, 5 (n = 29)			
	+	=	—	p	+	=	—	p	+	=	—	p	+	=	—	p
Hungry	2	3	10	0.05	4	9	3	...	5	4	4	...	9	13	7	...
Thirsty	3	6	6	...	8	5	3	...	4	4	5	...	12	9	8	...
On edge	6	4	5	...	3	10	3	...	3	6	4	...	6	16	7	...
Vigorous	3	3	9	...	8	7	1	0.05	5	5	3	...	13	12	4	0.05
Pensive	4	7	4	...	4	11	1	...	1	9	3	...	5	20	4	...
Drunk	7	7	1	0.10	2	12	2	...	2	11	0	...	4	23	2	...
Nonchalant	4	10	1	...	5	6	5	...	4	8	1	...	9	14	6	...
Efficient	5	3	7	...	7	8	1	0.10	5	7	1	...	12	15	2	0.05
Skeptical	6	6	3	...	4	9	3	...	2	8	3	...	6	17	6	...
Good-natured	1	7	7	0.10	3	9	4	...	2	9	2	...	5	18	6	...
Cheerful	3	5	7	...	5	9	2	...	3	8	2	...	8	17	4	...
Energetic	4	7	4	...	6	9	1	...	3	4	6	...	9	13	7	...
Anticipative	3	9	3	...	5	7	4	...	4	5	4	...	9	12	8	...
Insecure	6	6	3	...	3	11	2	...	2	9	2	...	5	20	4	...
Dizzy	9	5	1	0.05	5	8	3	...	4	8	1	...	9	16	4	...
Active	1	7	7	0.10	6	7	3	...	4	7	2	...	10	14	5	...
Peaceful	4	5	6	...	6	8	2	...	4	5	4	...	10	13	6	...
Industrious	1	6	8	0.05	6	7	3	...	4	5	4	...	10	12	7	...
Cautious	0	10	5	0.10	4	8	4	...	2	7	4	...	6	15	8	...
Drowsy	8	3	4	...	5	7	4	...	5	8	0	0.10	10	15	4	...
Sarcastic	2	8	5	...	4	10	2	...	4	4	5	...	8	14	7	...
Ambitious	2	7	6	...	5	10	1	...	6	5	2	...	11	15	3	0.10
Clear-headed	1	6	8	0.05	7	3	6	...	4	4	5	...	11	7	11	...
Quiet	5	7	3	...	7	6	3	...	2	4	7	...	9	10	10	...
Dopey	8	6	1	0.05	6	8	2	...	1	12	0	...	7	20	2	...
Happy	5	6	4	...	4	10	2	...	4	6	3	...	8	16	5	...
Relaxed	6	1	5	...	6	5	5	...	3	6	4	...	9	11	9	...
Weak	5	5	5	...	2	8	6	...	2	5	6	...	4	13	12	0.10
Moody	8	3	4	...	1	8	7	0.10	3	8	2	...	4	16	9	...
Light-headed	9	4	2	0.10	6	7	3	...	6	7	0	0.05	12	14	3	0.05
Elated	4	7	4	...	7	9	0	0.05	5	8	0	0.10	12	17	0	0.01
Obliging	5	5	5	...	5	11	0	0.10	6	3	4	...	11	14	4	...
Overjoyed	2	11	2	...	4	12	0	...	4	9	0	...	8	21	0	0.01
Self-controlled	2	7	6	...	4	8	4	...	2	9	2	...	6	17	6	...
Muddled	7	7	1	0.10	5	10	1	...	2	8	3	...	7	18	4	...
Exhilarated	4	8	3	...	6	8	2	...	4	8	1	...	10	16	3	0.10

* The dosage of secobarbital in experiment 1 was 100 mg. per 70 kg. of body weight; that in the other experiments was 50 mg. per 70 kg. of body various experiments. Only 36 of the 81 items are presented in this table, since the remaining 45 items did not yield significant differences in any com-

Amphetamine Seen as an Aid to Performance.—Seventy-seven per cent of the subjects performed better after taking amphetamine (14 mg.) than after taking placebo. The results obtained with the two "general questions" (tables 2 and 3) indicate that the subjects, considered as a group, did attribute more favorable effects to amphetamine than to placebo, but that the number of subjects (59%) who reported being helped more by amphetamine than by placebo was smaller than the number who actually performed better on amphetamine than on placebo days. It is possible that some of the 19 subjects (34%) whose answers to the "general questions" indicated no difference between the amount of aid given by amphetamine and placebo, actually did notice an improvement on amphetamine days but did not believe it was due to the drug. The data in table 4 bear on this possibility. Examination of the "detail questions" showing the most definite amphetamine-placebo differences reveals that (with the exclusion of the swimmers of the first experiment, whose atypicality will be discussed) the percentage of subjects reporting improvement on amphetamine days, with respect to at least some (four to seven) detailed aspects of performance, was about the same as the percentage actually exhibiting improvement.

Amphetamine Seen as Aiding a Variety of Factors.—Since the runners, swimmers, and weight-throwers were not, for the most part, asked the same "detail questions" on their questionnaires, it is difficult to give summarizing statements about the effects reported by all athletes considered as a single group. An over-all examination of table 4 does suggest, however, that amphetamine might aid athletic performance by influencing a variety of factors. The runners and swimmers (the weight-throwers were not asked this question) reported feeling more "revved up," or stimulated, before performance on amphetamine than on placebo days; the runners and weight-throwers reported having more strength and endurance on amphetamine days; and all three types of athletes reported having better coordination and form on amphetamine than on placebo days.

*of Secobarbital—Tabulation of Responses**

Secobarbital vs. Placebo, per Experiment No. (After Performance)																			
1 (n = 15)				2 & 3 (n = 16)				4 (n = 9)				5 (n = 13)				2-5 (n = 38)			
+	=	−	p	+	=	−	p	+	=	−	p	+	=	−	p	+	=	−	p
2	6	7	...	4	7	5	...	2	6	1	...	2	5	6	...	8	18	12	...
5	4	6	...	3	7	6	...	1	7	1	...	5	5	3	...	9	19	10	...
3	6	6	...	5	8	3	...	3	6	0	...	4	9	0	...	12	23	3	0.05
8	4	3	...	7	7	2	...	2	5	2	...	3	8	2	...	12	20	6	...
3	8	4	...	7	7	2	...	2	7	0	...	2	10	1	...	11	24	3	0.10
7	8	0	0.05	2	13	1	...	0	9	0	...	2	11	0	...	4	33	1	...
7	7	1	0.10	2	4	10	0.05	3	4	2	...	5	5	3	...	10	13	15	...
4	7	4	...	5	7	4	...	2	3	4	...	3	8	2	...	10	18	10	...
2	7	6	...	6	9	1	...	2	5	2	...	2	11	0	...	10	25	3	0.10
7	6	2	...	3	8	5	...	3	2	4	...	7	5	1	0.10	13	15	10	...
9	5	1	0.05	4	6	6	...	4	4	1	...	6	7	0	0.05	14	17	7	...
5	5	5	...	5	6	5	...	2	4	3	...	5	8	0	0.10	12	18	8	...
1	8	6	...	8	7	1	0.05	2	7	0	...	4	7	2	...	14	21	3	0.05
0	9	6	0.05	4	11	1	...	2	5	2	...	0	10	3	...	6	26	6	...
10	1	4	...	3	7	6	...	1	8	0	...	4	9	0	...	8	24	6	...
3	9	3	...	7	5	4	...	3	3	3	...	3	7	3	...	13	15	10	...
5	7	3	...	5	7	4	...	4	3	2	...	5	8	0	0.10	14	18	6	...
8	6	1	0.05	5	4	7	...	3	6	0	...	4	5	4	...	12	15	11	...
5	5	5	...	4	8	4	...	2	4	3	...	2	8	3	...	8	20	10	...
8	4	3	...	4	6	6	...	1	7	1	...	6	1	6	...	11	14	13	...
1	6	8	0.05	2	7	7	...	1	7	1	...	3	7	3	...	6	21	11	...
1	9	5	...	6	8	2	...	3	3	3	...	3	6	4	...	12	17	9	...
2	6	7	...	5	7	4	...	3	6	0	...	5	4	4	...	13	17	8	...
2	8	5	...	12	1	3	0.05	1	3	5	...	2	7	4	...	15	11	12	...
9	6	0	0.01	2	9	5	...	2	7	0	...	3	10	0	...	7	26	5	...
10	2	3	0.10	3	7	6	...	4	2	3	...	5	7	1	...	12	16	10	...
4	4	7	...	6	9	1	...	6	2	1	...	6	3	4	...	18	14	6	0.05
2	5	8	...	3	5	8	...	3	4	2	...	4	4	5	...	10	13	15	...
3	5	7	...	2	6	8	...	1	8	0	...	3	3	7	...	6	17	15	0.10
10	5	0	0.01	4	8	4	...	1	7	1	...	4	9	0	...	9	24	5	...
5	10	0	0.10	4	9	3	...	2	7	0	...	2	8	3	...	8	24	6	...
3	7	5	...	0	9	7	0.05	3	3	3	...	4	7	2	...	7	19	12	...
2	12	1	...	2	10	4	...	2	7	0	...	1	12	0	...	5	29	4	...
1	6	8	0.05	4	11	1	...	3	5	1	...	2	5	6	...	9	21	8	...
4	9	2	...	4	9	3	...	2	7	0	...	4	6	3	...	10	22	6	...
3	12	0	...	2	10	4	...	2	6	1	...	2	11	0	...	6	27	5	...

weight. The subjects of experiment 4 did not complete the check list before performance. See table 1 for other methodological differences among the parison.

Amphetamine and the Question of "All-out" Performance.—The results obtained with the "detail question" pertaining to whether the subjects gave an "all-out" performance were surprising. The weight-throwers, considered as a group, reported throwing more "all-out" on amphetamine than on placebo days, but the runners reported that their performances were less all-out on amphetamine days; neither group of swimmers reported a significant difference between amphetamine and placebo days with respect to this question. All three groups of athletes performed better on amphetamine than on placebo days, and yet only the weight-throwers reported giving more all-out performances on the amphetamine days. If the runners and swimmers did give more all-out performances on amphetamine than on placebo days, they did not appear to recognize it.

Secobarbital Mistakenly Seen as an Aid.—The responses to the "detail questions" made by the 38 runners and weight-throwers who were given 50 mg. of secobarbital did not yield any significant differences between secobarbital and placebo effects, but the answers to the "general questions" indicated that these 38 subjects, considered as a single group, did attribute more beneficial effects to secobarbital than to placebo. This was surprising, in view of the fact that secobarbital neither improved nor impaired the performance of this group of subjects to a significant degree. Even more surprising was the fact that the answers to the "detail questions" given by the 15 swimmers who took the 100-mg. dose of secobarbital indicated that they attributed highly beneficial effects to that medicament (when swimming alone), whereas the fact of the matter was that it produced a great impairment in performance. This latter finding indicates that the 100-mg. dose of secobarbital can, under certain circumstances, produce a marked distortion in judgment. In addition to the data presented above, other data providing a more precise and detailed analysis of this distortion were collected. A quantitative assessment of the amount of judgment distortion produced under various conditions by 100 mg. of secobarbital is presented, and the implications of these results are discussed, in a concurrently published paper.[4]

Possible Influences of Mood and Physical States on Performance.—The major effects of amphetamine on mood and physical states were increased physical and mental activation, elation, boldness, and friendliness. These effects, which were present both before and after performance, could reasonably be expected to favor good performance. This does not, of course, rule out the possibility that amphetamine aids performance by changing respiratory, cardiac, metabolic, or other physiological functions. Our data do not deal with these factors. In the third paragraph of this section, evidence was adduced to indicate that amphetamine might aid athletic performance by altering a variety of factors. The effects of amphetamine on mood and physical states give further support to that conclusion.

The major effects of 100 mg. of secobarbital on mood and physical states before performance were intoxication and "deactivation." These effects would seem definitely disadvantageous to performance. The major effects of 50 mg. of secobarbital before performance were mental and physical activation and elation. These effects are similar to some of those produced by 14 mg. of amphetamine and might be expected to contribute to an improvement in performance. Whether these effects did contribute to an improved performance but were counterbalanced by detrimental effects, or whether they actually did not influence performance, are questions which cannot be answered on the basis of the present data. All that can be said is that secobarbital (50 mg.) and amphetamine (14 mg.) were similar in certain of their effects on mood and physical states but that amphetamine significantly improved performance whereas secobarbital did not.

Differences in Results Obtained in the Various Experiments.—In general, the six experiments reported above were similar to each other with respect to the subjective effects produced by amphetamine and secobarbital. Two exceptions will be discussed. Table 6 indicates that, after performance, the weight-throwers of experiment 5 obtained 30 significant amphetamine-placebo differences on the check list dealing with mood and physical states, about four times as many as any other group of subjects. The weight-throwers obtained a greater improvement in performance from amphetamine than did the runners or swimmers (the weight-throwers improved from 3 to 4%, the runners improved about 1.5%, and the swimmers improved from about 0.6 to about 1.2%), and they were probably aware of this rather extensive improvement on amphetamine days because they were able to observe the distance of each throw. An awareness of the success of their immediately preceding performance might have contributed to their especially high degree of activation, elation, boldness, and friendliness after performing on amphetamine days.

The swimmers of experiment 1 were different from the remaining groups with respect to the effect of amphetamine on subjective responses pertaining to performance and with respect to subjective responses concerning mood and physical states. In spite of the fact that amphetamine significantly improved their performance, those 15 subjects did not evaluate it as having done so; they also did not report the effects on mood and physical states (increased activation, elation, boldness, and friendliness) which were reported by the other groups of subjects. The exact cause of this difference is not known; however, two factors which may be related to it will be mentioned. First, the subjects of that experiment were studied on consecutive days. It is possible that the drug comparisons were to some extent contaminated by "carry-over" effects. Second, chance sampling factors caused a bias in the amphetamine-placebo comparisons. The responses to the check list obtained each day before medicaments were taken indicated that the subjects, considered as a group, began their amphetamine sessions feeling less industrious, efficient, and clear-headed and more mentally cloudy than when they began their placebo sessions. They also felt more insecure, inhibited, skeptical, self-conscious, and pensive and less cheerful, good-natured, and self-controlled before taking amphetamine than before taking placebo. The comparison for "insecure" was significant at the 0.01 level with a two-tailed sign test, that for "cheerful" at 0.05, and those for "industrious" and "inhibited" at 0.10. The others just mentioned were at the 0.25 level of significance. Comparisons which reach the 0.25 level are not considered to be statistically significant in this report but are mentioned in the present context in an attempt to clarify the nature of the sampling bias.

Amphetamine and Antisocial Behavior.—Recently there has been considerable interest in the question of whether amphetamine produces "temporary alterations in personality" (changes in mood and behavioral predispositions) which might facilitate antisocial behavior. In a government report[5] the opinion was expressed that improper use of amphetamine is associated with problems of juvenile delinquency and crime. It was stated, "Investigation by authorities has determined that many lawbreakers have consumed 'thrill pills' to bolster their courage for commission of crimes." Viewed in this context, the fact that amphetamine is reported to be in widespread use by students, businessmen, and other noncriminal citizens becomes a matter of significance. The question arises whether amphetamine produces "temporary changes in personality" which might lead nondelinquent persons, such as athletes or students, to engage in antisocial behavior. The present study was not designed to answer that question, but the quantitative information concerning the mood effects produced in athletes by amphetamine is relevant.

In the present investigation, increased feelings of mental and physical activation, elation, boldness, and friendliness were the main effects of amphetamine on mood and physical states. Increased checking of drunk, impulsive, and satisfied was also found. The increase in effects classified as boldness and friendliness is pertinent to the issue of antisocial behavior; perhaps the increased checking of drunk and impulsive is also, since increases in these two effects may imply a reduction in self-control.

We cannot, of course, say that a person who reports feeling an increase in friendliness will always exhibit, simultaneously, an increase in friendly behavior or that one who reports an increase in unfriendly feelings will simultaneously exhibit an increase in antisocial behavior. It does seem reasonable, however, to assume that an increase in friendly feelings will increase the likelihood of friendly behavior on the average and, contrariwise, that an increase in antisocial feelings will increase the likelihood of antisocial behavior. It also seems reasonable to assume that in a group of cooperative subjects who are interested in the study conducted (such as the athletes of the present investigation appeared to be), reports concerning mood states would correspond to true feelings, in general. We must mention, however, that when drugs are given which might influence judgment (and in the present study secobarbital, 100 mg., was found to be such a drug) it is possible for behavior and reported feelings to be quite discrepant.

As shown in the figure, the athletes checked bold, boastful, cocky, self-confident, playful, and domineering more and insecure less on amphetamine than on placebo days. Those mood changes might, under certain circumstances, facilitate antisocial behavior, particularly the changes in feelings which account for the increased checking of cocky and domineering. However, the increased boldness was accompanied by greater friendliness, as indicated by more checking of friendly, talkative, good-natured, obliging, and trustful and less checking of grouchy, unsocial, and sarcastic. The psychological meaning and behavioral consequences of simultaneously increasing friendliness and boldness are not known. Furthermore, it is almost certain that such behavioral consequences would be strongly influenced by social and environmental circumstances. Additional work is needed to determine the frequency of the coexistence of friendliness and boldness, the circumstances in which it leads to antisocial behavior, the circumstances in which it leads to socially constructive behavior, and, in addition, the role of personality factors in such reactions. The data of the present investigation indicate that most nondelinquent persons who take amphetamine in a moderate dose, such as that used in the present study, and who do so in a situation in which social forces tend to inhibit rather than promote antisocial behavior, are likely to experience mood effects which contain both socially positive and socially negative elements.

Summary

Fifty-seven athletes (runners, swimmers, and weight-throwers) who were in middle or late season condition were given amphetamine (14 mg.), secobarbital (100 mg. or 50 mg.), or placebo on different occasions. The medicaments were given on a body weight basis, the doses just mentioned being those given to a subject who weighed 70 kg. (154 lb.). The subjects were given each type of medicament, orally, several times (three on the average). The medicaments were given in a counterbalanced order which was unknown to the investigator collecting the data and unknown to the subjects. After taking each medicament the subject performed his regular athletic event and afterward evaluated his performance, on a questionnaire containing 15 to 20 questions. In addition, each subject gave information about his mood and physical states by responding to an 81-item check list once before taking each medicament and twice afterward. The 57 subjects were studied 781 times in the above manner. Comparisons between amphetamine and placebo and between secobarbital and placebo were made with respect to answers to questions about the performances and with respect to responses to the check list dealing with mood and physical states.

The subjective responses of the athletes indicated that 14 mg. of amphetamine sulfate might improve athletic performance by influencing a variety of factors: the beneficial effects reported were increased stimulation (feeling "revved up") before the performance, improved coordination and form, increased strength and endurance, and increased mental and physical activation. Most athletes did not report that performances on ampheta-

mine days were more "all-out" than those on placebo days. Amphetamine increased feelings of boldness, elation, and friendliness; these mood changes contained both socially positive and socially negative elements. The 100-mg. dose of secobarbital sodium produced intoxication, elation, "deactivation," and distortion in judgment. The 50-mg. dose produced elation and activation.

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TREATMENT OF DERMATOSES WITH INTRAVENOUSLY GIVEN METHYLPREDNISOLONE SODIUM SUCCINATE

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Thirty-one different dermatoses were treated by intravenous administration of methylprednisolone sodium succinate to 242 patients. Despite the use of relatively large doses, none of the patients developed symptoms of adrenal atrophy or psychic depression. The usual dose per treatment was 20 mg., but some patients received 90 mg. daily for three weeks. Several patients with moon facies which developed during oral adrenal steroid therapy, previously prescribed, were relieved of this side-effect when the intravenous route of administration was used. When taken orally a percentage of this agent is thought to be converted to cortisone by the physiological activities of the upper gastrointestinal tract. This reaction is apparently obviated by intravenous or intramuscular administration, and the compound remains as methylprednisolone sodium succinate during its short life in vivo (half-life 188 minutes). Of the 242 patients treated only 18 had little or no improvement of their dermatoses.

Basic researchers and clinical investigators are constantly at work to reproduce and investigate new steroids in order to find a product which will cause the maximum good results and the minimum side-reactions. There is no advantage in using a product with increased anti-inflammatory potency per milligram of adrenal steroid compound unless the therapeutic index is concomitantly improved. Intravenously administered methylprednisolone sodium succinate, which was made available for this study in June, 1958, is a product with these characteristics. Since then we have treated 242 patients with 2,636 injections totaling 57,010 mg. of this drug. The age of these patients ranged from 6 months to 93 years. Preston and Flatt[1] used hydrocortisone and prednisolone hemisuccinate intravenously and focused their attention on 10 patients with severe dermatological conditions, in 9 of whom they reported a rapid response, using as much as 50 mg. of the drug two to three times a day for a total of 165 injections. They made no reference to attendant side-reactions. Since that time, intra-

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venously given adrenal steroid preparations have been commercially available but for the most part have been used only as emergency drugs.

Intravenously given methylprednisolone sodium succinate has the same potency, milligram for milligram, as orally given methylprednisolone sodium succinate. Its half-life is 188 minutes,[2] whereas the half-life of the orally given medicament is 345 minutes.[3] As far as we know, methylprednisolone sodium succinate has not been recovered as such from the urine, and when it is ingested orally 75% of the drug has disappeared by the time it reaches the lower part of the rectum. During our clinical investigation, we noted that despite the relatively large doses of intravenously given methylprednisolone sodium succinate used none of the patients developed symptoms of adrenal atrophy or psychic depression. Ninety-five per cent of the patients said that they had a feeling of well-being; 75% of the patients noted an increase in their appetite, and four patients became hyperactive and demonstrated mild euphoria, restlessness, and insomnia. Most of them felt as if they had increased amounts of energy. Several patients had developed moon facies while receiving oral adrenal steroid therapy. When these patients were given methylprednisolone sodium succinate intravenously the moon facies disappeared in a relatively short time even though they were receiving 20 mg. or more of the drug per day.

Following is a possible explanation of the phenomenon that despite the high dosage and the large number of intravenous injections of methylprednisolone sodium succinate there have appeared no severe untoward adrenal steroid side-reactions to date. Orally given methylprednisolone sodium succinate is a synthetic compound, and it is thought that in the upper gastrointestinal tract the methyl radical may be sheared off by the action of digestive juices and enzymes or by the interference of intestinal bacteria. As a result of this action, a percentage of the drug is converted to cortisone. When, on the other hand, the drug is given intravenously or intramuscularly, this action does not take place and the compound probably remains as methylprednisolone sodium succinate during its short period of life in the circulatory system.[4] We also believe that methylprednisolone sodium succinate produces its maximal effect when it is given intravenously.

Another suggestion has been offered by H. F. West of the Sheffield Center for the Investigation and Treatment of Rheumatic Diseases, Nether Edge Hospital, England. He has stated that the essential difference between intravenous treatment and the daily administration of oral corticosteroids is that the use of the former method raises the concentration of available corticosteroids above normal levels via the systemic route and allows the adrenal to work normally before the next dose is given. When 10 mg. of methylprednisolone sodium succinate is given by mouth daily, the adrenal involutes to some extent and adds a very small amount of corticosteroids to the circulation each day. West further believes that to measure the effective concentration of cortisol or prednisolone in the blood it is necessary to separate the protein-bound from the free steroids.[5]

The rapid response to treatment with methylprednisolone sodium succinate may sometimes be dramatic, whether the patient has a mild or serious disease. The optimal dosage is 20 mg. per treatment,

TABLE 1.—*Results of Use of Intravenously Given Methylprednisolone Sodium Succinate at Cincinnati General Hospital*

Dermatoses	Cases, No.	Dosage (Mg.)		Injections, No.	Results				Side-effects
		Effective	Total		Poor	Fair	Good	Excellent	
Pyoderma gangrenosum	1	20	850	95	0	0	0	1	None
Pemphigus foliaceous	1	30	2,010	85	0	0	0	1	Mild nervousness
Pemphigus vulgaris	1	30	1,330	51	0	0	0	1	Euphoria, insomnia
Exfoliative dermatitis	2	20	1,625	50	0	0	0	2	Mild euphoria
Infectious eczematoid dermatitis	5	10-20	1,250	74	0	0	0	5	None
Dermatitis venenata (vegetation)	4	10-20	200	11	0	0	0	4	None
Acute urticaria and angioedema	9	10-40	180	9	1	0	0	8	None
Psoriasis	5	20-30	4,080	209	1	0	0	4	None
Reactions to insect bites	10	10-40	210	10	0	0	4	6	None
Lichen planus	2	40	480	16	0	0	2	0	None
Bullous lichen planus	1	30	1,300	54	0	0	1	0	None
Lichen plano pilaris	1	20	560	28	1	0	0	0	None
Serum sickness	2	20	40	2	0	0	0	2	None
Alopecia areata†	2	20	400	15	.	..	..	1	None
Lupus erythematosus disseminatus	2	20	2,110	101	0	0	1	1	Furunculosis, increased appetite
Lymphadenosis cutis benigna with diabetes mellitus	1	20	450	36	0	1	0	0	Decreased glucose tolerance
Erythema multiforme	3	20	1,850	34	0	0	0	3	None
Allergic dermatitis	3	20	1,200	60	0	1	2	0	None
Neurodermatitis disseminata	1	20	320	16	0	0	0	1	None
Generalized granuloma annulare	1	20	1,850	119	0	0	0	1	None
Mycosis fungoides‡	1	40	280	7	..	..	..	..	None
Totals	52		21,510	1,177					

† Treatment discontinued in one patient.
‡ Improved.

but some patients have received 90 mg. per day for as long as three weeks. The frequency of injections decreases as the patient improves. Some patients have received the drug only once a week for as long as nine months. If the patient received the drug daily, no oral adrenal steroid medicament was given, but if methylprednisolone sodium succinate was given every other day or once a week the patient was given adrenal steroids orally in maintenance doses not exceeding 12 mg. per day or a depot injection of methylprednisolone acetate of 40 to 80 mg. per week. If the treatment is prematurely terminated or if maintenance oral therapy is not instituted because of the rapid response of the disease to medication, rebound reactions will occur. If the patient has inaccessible veins, one may resort to intramuscular administration. During this treatment, we noted little weakening of natural defenses against infection, while local and systemic disease manifestations were being suppressed.

This drug is a white powder, chemically known as sodium 6α-methylprednisolone-21-succinate, buffered with phosphate and containing lactose as a diluent. It is mixed with 1 cc. of distilled water. The desired dose, measured in milligrams, is withdrawn and is diluted further with distilled water in a syringe to a 2 cc. volume in order to facilitate its use. The medicament can stay in solution for at least a week without deteriorating, but after that time the solution becomes milky and flocculent. If given intravenously, the injection time is 20 to 30 seconds. There has been no attendant immediate or delayed reaction to the injection of the drug.

Fifty-two patients were treated at the Cincinnati General Hospital (table 1) and 190 patients in private practice (table 2). In these groups there were 31 different skin diseases. Some unusual responses were recorded.

The patient with scleroderma received over 6,000 mg. of combined orally and intravenously administered methylprednisolone sodium succinate, and there has been no progression in the disease since treatment was started. He is more than 70% improved. The patient with pemphigus foliaceous received 90 mg. of the drug per day for three weeks, at the end of which time there was no evidence of any cutaneous lesions. A total of three injections of methylprednisolone sodium succinate given intravenously at three-day intervals was sufficient to clear the skin of five patients with pityriasis rosea. Three of these patients were 60% improved after the first injection. Forty or more milligrams of injectable medicament per day was required to produce clearance of the lesions in patients with psoriasis. With this treatment some persons with the most severe cases of psoriasis can be markedly improved in 14 days. The patient with acute disseminated lupus erythematosus had three positive L. E. cell preparations prior to intravenous therapy with methylprednisolone sodium succinate. After 14

TABLE 2.—*Results of Use of Intravenously Given Methylprednisolone Sodium Succinate in Office Practice.*

Dermatoses	Cases, No.	Dosage (mg.)		Injections, No.	Results*			
		Effective	Total		Poor	Fair	Good	Excellent
Allergic dermatitis	13	20	580	251	1	0	2	10
Neurodermatitis	9	20-40	1,360	39	0	0	2	7
Reactions to insect bites	6	20	120	6	0	0	0	6
Dermatitis medicamentosa	9	20	1,280	52	0	0	0	9
Allergic eczematoid dermatitis	8	20	1,680	69	0	0	0	8
Contact dermatitis	22	20-40	2,310	96	0	0	0	22
Dermatitis venenata	12	20	1,120	44	0	0	0	12
Light eruption	3	20	420	21	0	0	0	3
Herpes zoster	4	20	840	42	0	0	0	4
Erythema multiforme	7	20	940	47	0	0	0	7
Lichen urticatus	1	20	100	5	0	0	0	1
Pruritus	9	20	720	35	0	3	0	6
Seborrheic dermatitis	15	20	3,020	131	0	0	0	15
Pityriasis rosea	5	20	280	14	0	0	0	5
Lichen planus	3	20	680	31	0	0	0	3
Lichen planus of the tongue	1	40	320	8	0	0	1	0
Psoriasis	18	40	8,200	74	4	0	4	10
Acute lupus erythematosus disseminatus	2	20-40	800	40	0	0	0	2
Subacute lupus erythematosus disseminatus	1	20-40	600	30	0	0	0	1
Postherpetic pain	4	20	460	23	3	0	1	0
Dyshidrotic dermatitis	2	20	760	38	0	0	0	2
Chronic lupus erythematosus	3	20	320	16	3	0	0	0
Pyoderma gangrenosum	1	30-40	1,200	40	0	0	0	1
Scleroderma†	1	20-40	3,200	160	..	..	..	..
Alopecia	17	20	3,320	91	0	0	0	17
Alopecia areata	5	20	3,320	91	0	0	0	5
Idiopathic alopecia of women	12	20	3,320	94	0	0	0	12
Inflammatory fungus infection	5	20	360	18	0	0	0	5
Leg ulcers‡	3	30-40	580	29	..	..	..	..
Totals	190		35,500	1,459				

* None of the patients treated showed side-effects.
† 70% improved.
‡ 60% improved.

days of such treatment, during which time the patient received 40 mg. of the drug daily, no L. E. cells were found in the peripheral blood smears. Because of the anaphylactoid reactions recently attributed to penicillinase, and our own good results in treating penicillin reactions with intravenously given methylprednisolone sodium succinate, we strongly recommend this compound for treatment of such dermatitis medicamentosa problems.[6]

This drug should be used judiciously along with the older and more conventional types of treatment. We do not depreciate the use of orally given adrenal steroids, but if large doses are required over a long period of time (more than 16 mg. of methylprednisolone sodium succinate or its equivalent a day for three weeks) or a rapid response to treatment is demanded, the intravenous use of methylprednisolone sodium succinate is strongly suggested.

Summary

The results of the routine treatment of 242 patients with 31 different dermatoses with intravenously given methylprednisolone sodium succinate were studied. A total of 57,010 mg. and 2,636 injections were given in a period of nine months. In this series of patients none developed symptoms of adrenal cortical hyperfunction (Cushing's disease) or any other severe reaction often associated with administration of adrenal steroid preparations. We have noted no osteoporosis, symptoms of adrenal atrophy, or psychic depression. No patient receiving intravenously given methylprednisolone sodium succinate has died either because of disease or trauma, so postmortem examinations have not been available to reveal any possible undisclosed visceral changes.

Patients who did develop symptoms of adrenal cortical hyperfunction on therapy with orally given adrenal steroid preparations lost their moon facies when given steroid treatment intravenously, despite the use of 20 or more mg. of methylprednisolone sodium succinate daily. The optimal dosage may vary from 20 to 90 mg. a day, and the treatment schedules vary according to the severity of the disease. We do not advocate discontinuation of oral adrenal steroid therapy, but we recommend the use of intravenously given methylprednisolone sodium succinate when large doses of adrenal steroid will have to be given for a long period of time or where a rapid response to treatment is demanded.

The lack of symptoms of adrenal cortical hyperfunction and other untoward adrenal steroid side-reactions in this series of patients, the acceleration of the anti-inflammatory effect in the therapeutic response of cutaneous disease, the reduction of required follow-up maintenance oral adrenal steroid medication, the elimination of long-term hospitalization, and the fact that continuous daily intravenous therapy with steroids is unnecessary renders routine treatment with intravenously given methylprednisolone sodium succinate in the office, home, or hospital a safe and practical procedure.

623 Doctors Bldg. (Dr. Goldberg).

The methylprednisolone sodium succinate used in this study was supplied as Solu-Medrol and the methylprednisolone acetate as Depo-Medrol by the Upjohn Company, Kalamazoo, Mich.

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ETIOLOGICAL FACTORS IN LEPROSY.—Climate, density of population and overcrowding are of secondary importance. Under natural conditions leprosy is not a children's disease. The age of onset is determined by opportunity for infection. Individual susceptibility or lack of resistance decide the issue whenever there is contact with infection. Lepromatous cases are grossly infectious but they are not the only, nor always the most important, sources of infection. Most patients, at some time or other, may be infectious to susceptible individuals. Prolonged intimate contact is not necessary. Susceptibility is a compound factor. Some or all of its components behave genetically. Susceptible individuals belong to a race within the race. They remain undiscovered until they react ineffectively to infection. The response of the host determines the form of his disease and, whilst there are strong resemblances between certain predominating patterns, not all fall easily into a simple classification. —J. A. K. Brown, M.D., Factors Influencing the Transmission of Leprosy, *International Journal of Leprosy*, July-September, 1959.

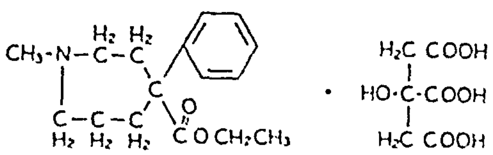
COUNCIL ON DRUGS

NEW AND NONOFFICIAL DRUGS

The following descriptions of drugs are based on available evidence and do not in any case imply endorsement by the Council.

H. D. Kautz, M.D., *Secretary.*

Ethoheptazine Citrate (Zactane Citrate).—1-Methyl-4-carbethoxy-4-phenylhexamethylenimine citrate.—The structural formula of ethoheptazine citrate may be represented as follows:



Actions and Uses.—Ethoheptazine citrate is a synthetic, non-narcotic analgesic of moderate potency allied structurally to meperidine. It has been used, in both ambulatory and hospitalized patients, for controlling mild or moderate pain associated with musculoskeletal disorders, such as arthritis, myositis, fibrositis, and ligamental strain; for neurological conditions, including neuritis, sciatica, and tabes dorsalis; for the immediate postpartum and postoperative period; and for the earlier stages of malignant diseases. Headache apparently responds poorly. The drug is ineffective in alleviating severe pain, such as that of myocardial infarction, renal colic, or the later stages of metastatic neoplasia. The analgesic effects of salicylates and ethoheptazine citrate are apparently additive; hence, the conjunctive use of the two may be more effective than either given alone. Such combined usage is especially desirable in rheumatoid arthritis, since ethoheptazine citrate apparently does not share the anti-inflammatory action of salicylates in this and similar conditions, nor has ethoheptazine citrate been shown to possess any antipyretic action.

Estimates of the analgesic efficacy of ethoheptazine citrate vary widely. Some clinicians report that it is about as effective as codeine, although one group has found it to be less effective in postpartum pain than aspirin given in single doses. In the only reported experiment in animals, ethoheptazine citrate was about one-third as active as meperidine.

The incidence of side-effects after usual doses of ethoheptazine citrate is relatively low. Epigastric burning, nausea, vomiting, dizziness, and pruritus are among those most commonly observed. Effects characteristic of opiates, such as sedation, suppression of cough, and depression of respiration, have not as yet been reported. Experimental administration of doses of 1.5 Gm. daily produced in some patients, after several days, symptoms suggesting cumulative toxicity, such as dizziness, visual disturbances, headache, syncope, and nervousness.

All of the experimental evidence and the results of clinical trial support the conclusion that ethoheptazine citrate is completely devoid of addiction liability. Nevertheless, the careless use of the drug is not justified, since experience with other analgesic agents has shown that habituation sometimes becomes apparent only after a drug has been in clinical usage for many years.

The metabolic fate and routes of excretion of ethoheptazine citrate in man are unknown. In animals, parenteral injection produced peak blood levels after about one hour. The drug was generally distributed, but highest concentrations were found in the liver. It was partially excreted by the kidneys, both as the unchanged compound and as hydroxy derivatives and deesterified derivatives. There was some evidence that the intestine was also a major route of excretion.

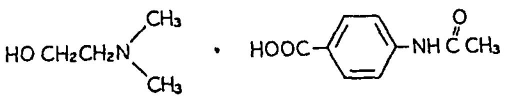
Dosage.—Ethoheptazine citrate is administered orally. The dose is 75 to 150 mg. three or four times daily, and it should be adjusted within this range in accordance with the severity of the pain and the response of the patient. Larger doses not infrequently produce undesirable side-effects; therefore, if the response to the stated dose is unsatisfactory, another, more potent analgesic may be preferred.

Preparations.—tablets 75 mg.

Year of introduction: 1958.

Wyeth Laboratories, Division of American Home Products Corporation, cooperated by furnishing scientific data to aid in the evaluation of ethoheptazine citrate.

Deanol Acetamidobenzoate (Deaner).—The *p*-acetamidobenzoic acid salt of 2-dimethylaminoethanol.—The structural formula of deanol acetamidobenzoate may be represented as follows:



Pharmacological Actions.—Deanol base is a tertiary amine which differs chemically from the quaternary amine, choline, only by the absence of one methyl group. Compared with choline, however, deanol more readily passes the blood-brain barrier. Deanol has been found to occur in the human brain in free and in bound form. In animals, intensive chronic oral administration of deanol results in excitatory effects on the central nervous system. In mice, the threshold for pentylenetetrazol-induced seizures is reduced, and spontaneous convulsions may occur. However, the thresholds for electrically induced convulsions and for seizures produced by strychnine are increased. A complex pattern of effects on the central nervous system has also been reported after administration of large intravenous doses of the drug to rabbits and cats.

Single large intravenously administered doses of deanol also produce cardiovascular effects. In anesthetized cats and dogs, blood pressure may be either increased or decreased. The depressor component can be antagonized by atropine; the pressor component has been attributed to release of catecholamines by the adrenal medulla. Under appropriate conditions, stimulation of sympathetic ganglions has also been demonstrated. The intimate mechanism of the central and peripheral effects of deanol remains to be established.

In man, deanol does not produce significant peripheral effects in the clinically recommended doses which are reported to exert effects upon the central nervous system.

Clinical Uses.—Deanol is proposed chiefly for the symptomatic relief of a wide variety of vague complaints, such as chronic fatigue, neurasthenia, and neurotic depression. It is also proposed for the alleviation of behavior problems and learning difficulties in school-age children. Besides being poorly defined, these symptoms are characterized by the difficulty in their evaluation, their spontaneous fluctuations, and their great susceptibility to suggestion. So far, the claims that deanol relieves these symptoms are based chiefly on uncontrolled clinical trials. The reported beneficial effects of the drug on mood and behavior remain to be confirmed by fully controlled studies in which placebos are administered. However, comparative studies in which the effects of the drug are contrasted with those of other medicaments appear to indicate a mood-alleviating effect attributable to administration of deanol. The reported influence of the drug on the behavior of children, in particular, appears to justify further study of its action for this purpose.

Toxicity and Side-Effects.—Clinical experience to date indicates that deanol is a drug of relatively low toxicity, and no serious side-effects have been noted with doses as large as 900 mg. daily. Occipital headache, constipation, muscle tenseness and spontaneous muscle twitching, insomnia, pruritus, postural hypotension, and weight loss have been reported in some patients. The relationship of these symptoms to the medication is uncertain, although they have been reported to disappear with decreased dosage. Although some benefit from deanol has been reported in children with electroencephalographic evidence of cerebral dysrhythmia, the drug may precipitate grand mal seizures. Accordingly, deanol is contraindicated in patients with grand mal epilepsy or in those with mixed seizures which have a grand mal component.

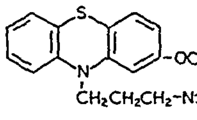
Dosage.—Deanol acetamidobenzoate is administered orally. Dosage is expressed in terms of the free base. Exact dosage for the drug cannot be stated. For adults, the proposed initial dose is 50 mg. daily; the proposed maintenance dosage ranges from 25 to 100 mg. daily. For children of school age with behavioral problems, the proposed initial dose is 75 mg. per day; the proposed maintenance dosage ranges from 75 to 150 mg. per day. Demonstrable effects usually are reported to be achieved only after several weeks of treatment.

Preparations.—tablets 25 mg.

Year of introduction: 1958.

Riker Laboratories, Inc., cooperated by furnishing scientific data to aid in the evaluation of deanol acetamidobenzoate.

Methoxypromazine Maleate (Tentone Maleate).—2-Methoxy-10-(3′-dimethylaminopropyl)phenothiazine maleate.—The structural formula of methoxypromazine maleate may be represented as follows:



$\cdot \begin{matrix} HC-CO_2H \\ \| \\ HC-CO_2H \end{matrix}$

Actions and Uses.—Methoxypromazine, a phenothiazine derivative, differs chemically from chlorpromazine only in that the chlorine atom of the latter compound is replaced by a methoxy radical. As might be expected from the chemical relationship, the biological actions of the two compounds are similar. (See the monograph on chlorpromazine hydrochloride in New and Nonofficial Drugs.) Thus, methoxypromazine maleate appears to be a member of that class of central depressants that alleviate anxiety and agitation and suppress aggressiveness, overtalkativeness, and other manifestations of motor excitement, without producing excessive sedation. Methoxypromazine, like meprobamate, finds its greatest usefulness in patients in whom these symptoms occur in mild form as part of nonpsychotic ambulatory psychiatric disorders. In psychotic patients with severe agitation and anxiety or markedly increased psychomotor activity, it is apparently less effective, in equal or even in higher doses, than is chlorpromazine. Thus, although favorable results have been reported in various psychoses, including manic states, delirium, agitated depression, and schizophrenia, many patients in these groups fail to respond. Further clinical trials, and particularly controlled studies, are needed to establish the relative value of methoxypromazine maleate in comparison with other agents now in use in psychiatric practice. The drug has also been used in treatment of various dermatoses associated with anxiety, but the number of reported cases is too small to permit any definite conclusions as to its value.

On the basis of early reports, side-effects seem to be somewhat less troublesome with methoxypromazine than with chlorpromazine, although sedation seems to be somewhat more marked than with the latter. Vertigo, palpitation, dryness of the mouth, constipation, hypotension, skin eruption, and aggravation of preexisting depression have, nevertheless, been reported. The Parkinson-like syndrome sometimes seen with other phenothiazine derivatives is rare and has occurred only when large doses were used. Granulocytopenia and jaundice have not yet been reported with methoxypromazine maleate, but the number of patients in whom it has been studied is too small to justify the assumption that such effects will not appear when it receives more extensive usage. Therefore, all patients receiving the drug should have periodic blood cell counts and should be carefully observed for evidence of other serious toxicity.

The pharmacological effects of methoxypromazine maleate resemble those of chlorpromazine. In experimental animals, the drug interferes with conditioned reflex activity, lowers the threshold for electroshock-induced seizures, potentiates ether and barbiturate anesthesia, produces adrenergic blockade, antagonizes the effects of serotonin, produces hypothermia, has some hypotensive activity, and reduces the volume and acidity of gastric secretion.

Dosage.—Methoxypromazine maleate is administered orally. The dosage must be adjusted in accordance with the response and tolerance of the individual patient. An initial dosage of 30 to 100 mg. daily, in divided doses, may be tried in nonpsychotic patients with mild emotional disturbances; more severely disturbed patients may require 200 to 500 mg. per day.

In psychotic patients an initial trial of 200 to 500 mg. daily is suggested. Although some patients have tolerated as much as 1.5 Gm. per day, it has not been clearly established that increasing the dose above 500 mg. per day improves the clinical response.

Preparations.—tablets 10, 25, and 50 mg.

Year of introduction: 1959.

Lederle Laboratories Division, American Cyanamid Company, cooperated by furnishing scientific data to aid in the evaluation of methoxypromazine maleate.

COUNCIL ON FOODS AND NUTRITION

ANNOUNCEMENT

The Council has authorized publication of the following report.

PHILIP L. WHITE, SC.D., *Secretary.*

A symposium "Nutrition in Tooth Formation and Dental Caries" will be held in Boston, May 19, 1960. This symposium, which will be an integral part of the annual meeting of the Massachusetts Medical Society, will be sponsored by the Council on Foods and Nutrition with the cooperation of the Harvard School of Dental Medicine; Massachusetts Medical Society; and the Massachusetts Dental Society.

The half-day program, which will begin at 9 a. m., Thursday, May 19, will be held in the Bay State Room of the Statler Hotel. The meeting is open to all interested persons, and there will be no registration fee.

The following program has been arranged.

9:00 a. m. **Welcome.** *Chairman:* JOHN B. MACDONALD, D.D.S., M.S., Ph.D., Harvard School of Dental Medicine and Forsyth Dentral Infirmary.

9:10 a. m. **General Introduction: Factors Controlling the Incidence of Dental Caries.** JAMES H. SHAW, Ph.D., Harvard School of Dental Medicine.

9:30 a. m. **Influence of Nutrition and Genetics on Tooth Size, Morphology, and Caries Susceptibility.** K. J. PAYNTER, D.D.S., Ph.D., Faculty of Dentistry, University of Toronto, Toronto, Canada.

10:00 a. m. **Chemical Agents Affecting Experimental Caries.** ISADORE ZIPKIN, Ph.D., National Institute of Dental Research, National Institutes of Health.

10:30 a. m. **Metabolism of Fluorides.** HAROLD C. HODGE, Ph.D., School of Medicine and Dentistry, University of Rochester.

11:00 a. m. **Cariogenicity of Foods.** BASIL G. BIBBY, D.M.D., Eastman Dental Dispensary, Rochester, N. Y.

11:30 a. m. **Discussion.**

MEDICINE AT WORK

- *Health—Country Style*
- *Who's in Charge?*
- *Patients and Education*
- *Speed and the Ambulance*
- *The Lead Detectives*
- *Bright Young Minds*

The Exhibitor

The scientific exhibit is a familiar part of most medical meetings. It is a form of scholarship regarded highly by the profession. Those who have not exhibited usually wish that they could, and those who have had the experience generally commend it to their peers.

Often left unsaid in these exchanges are some of the drawbacks encountered in exhibiting. But Dr. Mark I. Hewitt, writing in a recent issue of the *Journal of the Indiana State Medical Association*, notes that there are side-effects produced by exhibiting and that these, while usually subclinical, can be upsetting. Such side-effects, he says, are personified, as follows:

The Proofreader—He stares, not at the exhibitor but at the exhibit itself, for lengthy periods. This may induce near-panic in the uninitiated exhibitor who feels he is faced with a paragon of medicine. When the comment finally comes, however, it is usually, "Do you know that you have an inverted comma in the footnote to panel three?"

The Changer—Onset may be precipitous or gradual, but if precipitous usually manifests "pseudochoreic sign." If recognized, the side-effect usually whispers, "Do you happen to have any dimes?" or, "Change for a quarter?"

The Sitter—He stays as long as four hours in a chair at the booth, meets all his friends, eats lunch out of a paper bag, and finally becomes so identified with the exhibit as to begin to answer questions and pass out literature.

Farms and the Family Doctor

Health Is Booming In the Nation's Rural Areas

Led by a farmer, a group of volunteers in Clinton County, Ohio, a decade ago interviewed 5,400 families and learned that only 60% of the school-age children were adequately immunized. The citizens, believing that a survey without action would be futile, tackled the problem. Within two years 95% of the youngsters were properly immunized, through the efforts of private physicians, an agricultural extension health educator, and other community leaders, working with health and education boards. Then the volunteers, still unwilling to rest, extended the immunization program to preschool children.

The Clinton story was retold at the A. M. A.'s 15th National Conference on Rural Health as being appropriate to the conference theme, "Meeting Challenges with Responsibilities." The meeting, for which 410 persons registered at Grand Rapids, Mich., Feb. 25 to 27, centered on discussions of medical careers away from the big cities, health care of farm families, and the best use of livestock and other agricultural products.

Contrary to a widespread notion, farm folk often are in closer touch with their doctors than are their city brethren. This point was made by Dr. E. Vincent Askey, President-elect of the A. M. A., speaking at the conference banquet. He cited a magazine survey in Iowa of several hundred rural families. Seventy-four per cent said they had no difficulty in getting a physician to come to their farm, 78% lived but 1 to 9 miles from a doctor, and only 1% were more than 30 miles away. "In Los Angeles, where I practice," Dr.

Interpersonal give-and-take characterizes extracurricular science sessions being offered to exceptional students in many of the nation's high schools. See story on page 1528.

Askey said, "many doctors think nothing of having to drive 10 miles to make a house call."

Dr. Askey said that, ironically, some farm families are "too busy" to protect their health at the very time when they have easier access to good medical care than ever before in history. He urged every farm family to have a personal physician, who will keep the family medical history, make regular physical check-ups, and give immunizations. "It hurts the office or factory when the manager is laid up, and it hurts a farm even more so."

Immunization problems of particular interest to rural areas were discussed by Dr. David E. Price, chief of the Bureau of State Services, U. S. Public Health Service: "In the large cities, we think of the promotion of immunization programs as a joint responsibility of medical societies and organized health departments. In rural communities . . . the partners are often different. Most successful rural programs have been sparked by the local physicians and members of lay organizations."

Dr. Price said that tetanus, although comparatively rare, has its highest incidence among agricultural workers. It also is a risk among babies in home deliveries, which occur most frequently in rural areas, especially in the southeastern United States. This same area is the last stronghold of diphtheria. While there has not been a confirmed case of smallpox in the United States since 1953, it occurs sporadically in Mexico and migrant workers pass through 47 of our 50 states every year.

Eating Habits Unknown

The total production of American farms can be tabulated in tons of grain and meat, dozens of eggs, and quarts of milk. How much will this information tell about the eating habits of individual persons? Very little, the conference was told by Dena C. Cedarquist, Ph.D., head of the Department of Foods and Nutrition at Michigan State University. She said that people vary so much in their diets that averages are practically meaningless. Records kept of what students eat, according to Dr. Cedarquist, often are of little value because of the desire to please the record keeper. She said, "Much of the food faddism comes from dietitians like myself," whose advice is misinterpreted.

S. L. Kalison, DVM, extension veterinarian at Virginia Polytechnic Institute, said he believes that too many chemical and drug additives, which have not been thoroughly tested, are being placed in livestock and poultry food for the purpose of increasing production, not for the prevention or cure of disease. He said farm production must be increased by at least 35 or 40% by 1975 to provide an adequate diet for the estimated population of the United States then. He said the assurance that livestock products are safe and wholesome is a joint responsibility of veterinarians, physicians, public health services, and county, state, and federal regulatory agencies.

Dr. Paul M. Bancroft, a Lincoln, Neb., pediatrician, who has been closely associated with 4-H Club work, said, "So much of what we know about foods and nutrition has been learned in the farmyard. . . . But there is a danger in applying this knowledge to humans." He said animals grow rapidly and reach maturity early, in contrast to children, who grow more slowly and unevenly while developing emotionally and spiritually.

You Don't Have to Be Old To Be a Country Doctor

A reminder that there are young country doctors was heard at the A. M. A.'s 15th National Conference on Rural Health. Dr. Jack L. Gibbs, speaking on his five years of general practice in Havana, Ill. (population 4,500), urged increased efforts to acquaint medical students and new physicians with advantages small towns offer.

A young man who receives a full and fair picture, Dr. Gibbs said, will become convinced he can provide good medical care in the rural community. . . . If he serves his community well, he will enjoy a personal and professional status that would be the envy of his colleagues in the city. . . . He will reach his patient capacity and financial security sooner. . . . He will find that he is closer to cultural and recreational facilities than he expected, and he will have a chance to help his community develop those that are lacking.

Dr. Gibbs is one of 32 physicians who, according to a count made last fall, are in rural practice in his state after receiving a medical education under a scholarship-loan program sponsored jointly by the Illinois Agricultural Association and the Illinois State Medical Society. Each of them received a $5,000 loan—in $625 installments for each semester in medical school. They are among 122 students who signed contracts since 1948, including 8 now in

As Near as the Phone

Nearness to a doctor may mean miles, minutes, or personal relationship. The vast majority of Iowa farmers polled by *Wallace's Farmer* indicated a closeness to their physicians on all three points.

Here are the questions the magazine asked and the replies of rural families:

Do you have difficulty in getting a doctor to come to your farm on house calls? Seventy-four per cent said they had no difficulty.

How far away is your nearest doctor? Seventy-eight per cent said 1 to 9 miles; 19%, 10 to 19 miles; 2% 20 to 29 miles; and 1% 30 miles or more.

military service, 17 who are interning, and 57 either in medical school or scheduled to enter this year. All of them agreed to practice for at least five years in a community of less than 5,000 population. During that period the loans are repaid at 2% interest. No money has been lost and repayments now are being used to finance new loans.

The Havana physician said, "Had it not been for the scholarship and loan I probably would not be a doctor today, or at least not a doctor in a rural community." When he started practice he borrowed $300 to redecorate an office over a hardware store. His only medical equipment was a stethoscope, blood pressure cuff, and reflex hammer. His wife, a registered nurse, was his nurse, bookkeeper, and receptionist. The nearest hospital was 20 miles away and consultants in most specialties 50 miles away. Later he obtained a partner, a former classmate, and they moved to a larger, better equipped quarters. The community has erected a 50-bed hospital, being paid for out of local taxes. Dr. Gibbs says:

"I am convinced that people want a family doctor . . . just as they want a family druggist, minister, or dentist. The medical interests of a people are best served when care is initiated promptly in the community."

Who's in Charge Here? Tennessee Lays down the Rule

In the confusion created by serious traffic accidents, lines of authority often blur and sometimes disappear in a fog of conflicting responsibilities. Sparked by an accident case in which an ambulance driver had delayed transporting an injured victim to the hospital, Tennessee doctors requested that medical authority in such cases be clarified.

In response to a letter from the Nashville Academy of Medicine, state Safety Commissioner Greg O'Rear recently issued a general order to all members of the Tennessee Highway Patrol that established physician authority in definite terms. The order reads:

"If a doctor of medicine is at the scene of an accident in which one or more persons have been injured, he should advise the law enforcement officer in charge of the investigation what, in the physician's professional opinion, should be done in order to assure the most prompt and beneficial medical attention for the injured person or individuals. Our trooper then shall instruct the ambulance driver and attendant to comply with the physician's advice and see to it that this instruction is carried out."

The medical protest was triggered by an ambulance driver's refusal to remove an injured victim to the hospital until the dead body of a second victim was removed from the wreckage.

Doctor Aids Dentist in Preparedness for Disaster

There is probably not a disaster plan chairman in the nation who hasn't sketched in, at least mentally, the emergency medical care potential embodied in his community's corps of dentists. But pragmatic planning for the training of these dentists, and their inclusion in emergency medical teams, has not been widespread. In fact, the dental profession has occasionally complained that although its members are frequently reminded of the importance of their emergency roles, disaster plan officials often fail to provide such training opportunities.

Whatever the problem nationally, however, this training is being offered in some areas. Most recent of the efforts took place in Atlantic City where a half-dozen physicians, led by Dr. David B. Allman, a former president of the A. M. A., offered a course in disaster medicine that attracted two-thirds of the membership of the Atlantic County Dental Society. What's more, it was a repeat performance requested by the dentists who had prevailed on Dr. Allman to put on such a course once before.

Six sessions were held on consecutive evenings. Each session included an introduction to the subject by Dr. Allman, a one and one-half hour lecture, and a question period. Subjects covered included wounds and triage; burns, airway problems, and tracheotomy; shock and blood fluids; fractures; and radiation—effect, detection, and decontamination.

Dr. Allman, a stout advocate of disaster planning, has headed the civil defense committee of the Medical Society of Atlantic County since its inception. He is also chief of emergency medical service for the Civil Defense Council of Atlantic County. In this capacity, he has seen to it that two dentists have been enlisted for each of the 10 emergency medical service teams that have been formed.

"We didn't make doctors out of any of them in that short time," said Dr. Allman, referring to the 45 dentists who took the course, "but we think it did a lot of good. Every session found them full of questions, causing many of the meetings to run over the allotted time." Speakers at the sessions were all associates of Dr. Allman's at Atlantic City Hospital. They included Drs. Morton W. Leach, James H. Mason IV, Paul H. Steel, Morton Rosenblatt, Daniel DeMeo, and Joseph Ackerman.

Dr. Allman not only supports the idea of medical preparedness for disaster but plugs the idea of interdisciplinary cooperation toward this end. "I'm available to any group that wants to plan a similar course," he says.

Tribute to Flexner

Medical Educators Continue The Search for Excellence

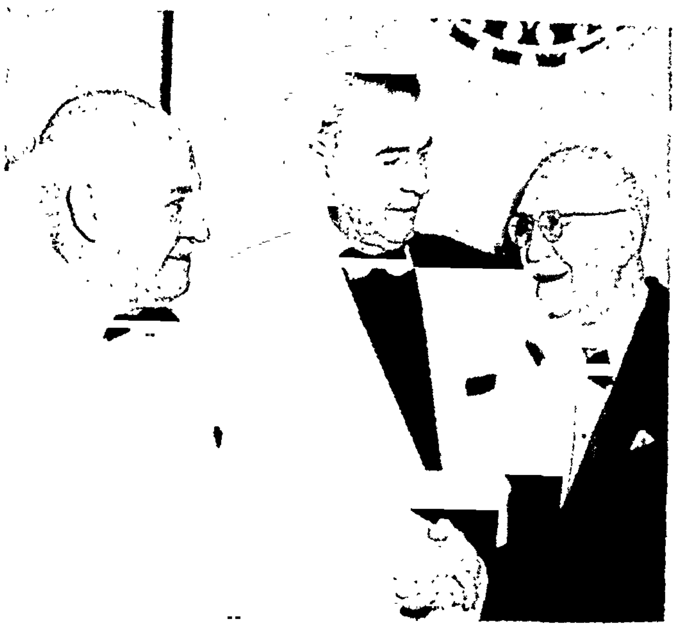
Lewis L. Strauss called him "the apostle of excellence," and Dr. Louis Orr noted that at the time of his death a newspaper had termed him "a mover and a shaker of his era." Medicine—50 years after he had diagnosed its ills—was honoring Abraham Flexner.

The setting could hardly have been more appropriate. Twelve hundred delegates were in Chicago to work toward improvement in the quality of medical education in the United States, a task which Dr. Flexner had undertaken singlehandedly a half-century before, with profound results. They were attending the 56th Annual Congress on Medical Education and Licensure, and they were considering, among other things, medicine's role as a university study and tomorrow's medical student, subjects sure to have appealed to Abraham Flexner.

Mr. Strauss, president of the Institute for Advanced Study founded by Dr. Flexner, noted that the pursuit of excellence had epitomized the educator's life, and he quoted Dr. Flexner on the point: "Mediocrity must not set the standard. Let us do for it all we can; perhaps even shake it out of itself, but let us not blind ourselves to the fundamental distinction between mediocrity and excellence."

In his tribute, President Orr reminded his audience that the city in which they were meeting was once described by Dr. Flexner as "the plague spot of the country" in his denunciation of the state of medical education in 1909. "This report," said Dr. Orr, "was a modest sized volume written in precise language, [but] its contents were so damning that within months of its release nearly half of the schools had to shut down."

As though to emphasize that the spirit of constructive criticism exemplified by Dr. Flexner had not atrophied, Congress speakers came prepared to put the finger on a number of what they considered to be weak spots in the educational process that produces physicians. Some selected comments follow:



Presidential meeting—medical officialdom is well represented at the Congress as Dr. Edwin H. Lawson, past-president of the Federation of State Medical Boards (*left*), and Dr. Louis Orr, A. M. A. President, welcome Dr. Walter L. Bierring (*right*), a former A. M. A. President.

On Patient Care in Basic Medical Education

Patients when they enter a hospital are afraid—afraid in many different ways, regardless of how brave a front they put up . . . Fear and a sense of complete dependency exist in one form or another . . . This is something that is occasionally forgotten, even at the better teaching hospitals.

Guy S. Hays, M.D.
Rockefeller Foundation

Most of us have become tired of hearing a medical school compared to a stool with three legs representing education, research, and service. In these days of research grants, we are inclined to forget that the single central function of a medical school is education. It is possible for a school to have too much research and too much service . . . When a medical school is given clinical responsibility which exceeds its resources, it is generally the educational program which first suffers.

Arthur Richardson, M.D.
Emory University

It has become the acknowledged aim of most medical schools to produce what has been variously termed the basic doctor or the undifferentiated doctor . . . the provision of broad knowledge which will permit the graduate to become with further training a good general practitioner, a specialist, a

Loans to Staffers

The perennial problem of resident pay is quite probably one for which the perfect solution will never be found. This has not, however, prevented an almost continuous search for some form of partial solution.

It is in this vein that the Merck Company Foundation recently established a $400,000 memorial loan fund for interns and residents. Those eligible will include members of the house staffs of 48 hospitals affiliated with 18 medical schools.

Between 75 and 100 interns and residents are expected to benefit each year from the fund, which is designed to become self-sustaining after eight years.

research worker, or a teacher. The aim is clear and not controversial. The path to its achievement has been less clear, and subject to much experiment.

Robert C. Dickson, M.D.
Dalhousie University

On Patient Care in Education Beyond Medical School

The exhausting efforts of medical faculties to improve undergraduate medical education have diverted, at least in certain instances, the attention of clinical teachers from problems of graduate education. This has been unfortunate. When the faculties of the medical schools accept the same enthusiastic responsibility for graduate education that they have accepted for undergraduate education, significant advances and improvements in the education of a physician are inevitable.

William D. Holden, M.D.
Western Reserve University

The environment of this [clinical] training has gone through many cycles. It has shifted back and forth from the classroom to the bedside. The importance of learning clinical medicine from the patient became established in medical education by Osler . . . [His] contributions and the Flexner report have established the ward and the clinic as the areas of clinical teaching in America.

Samuel P. Martin, M.D.
University of Florida

The physician is a natural student. He has no other way of life . . . [But] he loses the habit of study for many reasons: It takes from three to five years to build a practice; he is usually building a family at the same time; he can't afford to go away for refresher studies and stimulation during these years; a formal educational program is usually not found in small hospitals; the stimulation for academic study is submerged in more and more work until there is time for nothing else . . . How does one avoid these traps? Foster a do-it-yourself educational program in your own hospital.

George J. Robertson, M.D.
Waterville, Maine

On Medicine As A University Study

Today in the United States, medical education is undoubtedly at a level very much improved over that of the pre-Flexner days. The question is how much of it is at a true, graduate university level. Putting semantics aside, one may well question the extent to which medical faculties in America have made medical education an opportunity for genuine study rather than a series of drill sessions for hopeful artisans . . . Medical schools vary widely in the quality of independent scholarliness which they encourage and inculcate in their students.

Maurice B. Visscher, Ph.D., M.D.
University of Minnesota

I come with little faith that you will find in what I have to say any great novelty or great erudition. But in spite of this latter fact I have strong conviction that we do need a reminder of what the hallmarks of the university are . . . the commitment to intellect . . . the principle of free inquiry in the search for truth . . . a concern for means and ends [and] finally . . . its concern for cultural synthesis, for the unity of knowledge, whether promoted by scholarship, discovery or invention.

Nils Wessel, President
Tufts University

On Tomorrow's Medical Student

How are we to select future physicians? Perhaps we labor under an operational concept which I shall call the psychology of prescription . . . a self-proving proposition. Upon examination, ingestors of our prescription can perform adequately within the confines of our own value systems, that is, they have learned to sit, think, and give the same answers as we. But this hardly proves the worth of our sys-

The Duty of Discipline

State medical licensing boards have historically had a dual function: (1) to test and pass on the qualifications of prospective licentiates and (2) to police the actions of those already engaged in the practice of their art.

This year, the Federation of State Medical Boards, meeting during the Congress on Medical Education and Licensure, heard a panel discuss such disciplinary areas as mental illness, narcotic's addiction, and income tax evasion. These are some of the comments expressed:

—In 17 states, commitment to a mental institution constitutes grounds for automatic revocation or suspension of a license to practice; in 21 states such action is not automatic; and in 9 states a license can be suspended or revoked only after a hearing.

—Physicians have not only the highest rate of narcotics addiction of any occupational group but also the highest recovery rate. The physician soon realizes his precarious position, and with proper treatment he can break the habit . . . He knows the discomfort and the anguish of withdrawal treatment, and the threat of recidivism.

—Of 43 states responding to a questionnaire, 30 reported that income tax evasion was a matter of concern to boards of medical examiners, and that conviction could or did result in revocation or suspension of license. In Idaho, however, licenses revoked for income tax evasion have been ordered reinstated by the State Supreme Court.

tem. It cannot be stated with any conviction that we critically examine our own value systems or our own self myths with the same energy and enthusiasm that we give to the task of compounding educational prescriptions.

Raymond Bunge, M.D.
Iowa State University

On the basis of the interest that has been shown in the consultant group's report, I believe it is safe to predict that Congress will consider proposals for aid for expansion of medical school facilities. And while I am not willing to predict what the decision will be, I will go this far: I don't believe there is any time to be lost in getting the planning underway. It will not be accomplished quickly or easily, and so much depends on it. Contemplate, if you will, the consequences of not making careful plans. Or the consequences of not meeting the growing demand for physician services.

William Stewart, M.D.
U.S. Public Health Service

Now let us take a look at the debits . . . the factors which deter students from the practice of medicine . . . One of these deterrents is the long course of education necessary before the student becomes an income-producing member of the profession. In my personal experience, every time I hear this subject discussed at medical meetings, we end up with one more year added to the total medical curriculum.

James Z. Appel, M.D.
A. M. A. Trustee

Chairman of the Council on Medical Education and Hospitals is Dr. Leland S. McKittrick of Brookline, Mass. Vice-chairman is Dr. W. Clark Wescoe of Kansas City, Kan. Other members are Drs. James M. Faulkner of Cambridge, Mass.; Warde B. Allan of Baltimore; John Z. Bowers of Madison, Wis.; W. Andrew Bunten of Cheyenne, Wyo.; Guy A. Caldwell of New Orleans; John W. Cline of San Francisco; Harlan English of Danville, Ill.; and Charles T. Stone of Galveston, Texas. Dr. Walter Wiggins is staff secretary.

Ambulance Service—Danger In the Errand of Mercy

Three ambulances that never reached their destinations made news early this year. Two were traveling separate routes in Chicago when they entered an intersection at approximately the same time and collided. A passenger, injured in an earlier accident, and one of the ambulance drivers died. A week later an ambulance and a car collided at Richmond, Va. A female patient and a rescue squad member who was administering oxygen died.

The four deaths are a small portion of the total which will occur this year from traffic mishaps. But thousands of injured persons, before being seen by a physician, will receive emergency treatment and transportation from laymen who are strangers to them. How good is the care? Are the ambulances properly equipped and the attendants fully trained?

Some widespread deficiencies have been reported on the basis of a survey made jointly by the American College of Surgeons, the American Association for the Surgery of Trauma, and the National Safety Council. Questionnaires were submitted in 1,560 cities. Replies were received from 865 (one in Canada), with a population of 58 million. The population of 19 of the cities was over 500,000, of 205 between 50,000 and 500,000, and 641 between 10,000 and 50,000. A joint policy committee commented on the following shortcomings:

Wrong Type of Vehicle—Reporting cities had 9,906 vehicles available for transportation of injured persons. The fact that 46% of the vehicles were ordinary patrol cars "implies inferior transportation," because the sitting position is hazardous for moving persons with many types of injuries. Another 46% of the vehicles were ambulances and 8% were dual-purpose patrol cars.

Lack of Equipment—Every vehicle used for transportation of injured persons should be equipped for at least four first-aid procedures. Yet, of the ambulances, 30% were unequipped for splinting fractures, 27% for controlling hemorrhages, 21% for dressing wounds, and 15% for administration of oxygen.

Inadequately Trained Personnel—At least two persons at each accident scene should have first-aid training equivalent to the Red Cross advanced course, with a yearly refresher. One of the persons may be the ambulance driver and the second an attendant, policeman, or fireman. Although about 60% of the cities with over 50,000 population claimed near-perfect handling of the injured at the scene, the self-appraisal paints a better picture than the joint committee believes actually exists.

Ineffective Laws—Considerable confusion was found over state laws and local ordinances setting requirements for first-aid equipment that ambulances must carry and training and abilities that drivers and attendants must have. The committee plans a future study to determine what laws actually are in effect and may draft model ambulance laws.

A local ordinance requiring first-aid training of ambulance workers was in effect in 105 of the 865 cities, and such a state law in 145 cities. About 95% of the reports received indicated that state or local laws give ambulance drivers special privileges to exceed speed limits or disregard traffic signals. The joint committee recommends that ambulances be regulated the same as other vehicles and asserts:

"Speed is seldom, if ever, a factor in the preservation of a life. The excessive speed of ambulances has been shown to result in more traffic deaths than lives saved."

The Lead Detectives Are At Work in Cincinnati

Each and every morning, 365 days a year, medical secretaries leaf through the new admissions charts on the pediatric wards of three Cincinnati hospitals. With this task completed, they report by phone to AVon 1-2731. Often the reports are negative, but there are also those days when the word goes out—possible or probable lead poisoning.

AVon 1-2731 is the number of Cincinnati's newly formed Lead Information Center, a rallying point for the assembly, classification, and dissemination of information on lead absorption and lead poisoning. The Center is the creation of 15 Cincinnatians who met last fall to seek an answer to the city's statistical upswing in lead poisonings, particularly in children. In 1946, Cincinnati recorded only one fatal case of lead encephalitis, yet in 1959, 72 cases of lead poisoning were reported, and 5 of the victims died.

Does this mean that lead absorption is increasing at such a rapid rate? Not likely, according to Dr. John E. Allen, medical director of the Convalescent Hospital for Children, who says, "This alarming increase reflects only our increased awareness of the disease and improved community facilities to detect cases. Undoubtedly hundreds of cases of lead poisoning have been undiagnosed in the past, many of these fatal."

Included in the 15 persons who met to form the Lead Center were representatives of just about every Cincinnati agency with an interest in the health and well-being of the city's residents. The Center's stated purpose is to coordinate the activities of all community elements engaged in the diagnosis, treatment, and prevention of lead poisoning in children. A report of suspected lead poisoning sets in motion a chain of connected events. First, the city health department sends both a nurse and a sanitarian to the child's home. Their reports are then circulated to the initiating hospital, the family physician, and the Lead Center.

Blood specimens from the patient and paint samples collected by the sanitarian are sent for analysis to the Kettering Laboratory, an investigative unit of the University of Cincinnati, headed by Dr. Robert A. Kehoe, a physician with a world-wide reputation in the handling of lead problems. The Kettering reports go to the hospital, the private physician, and the Lead Center.

When all reports are in, the Center transmits names of all patients with elevated blood lead levels to the health department, and checks with the initiating hospital to insure adequacy of patient care and follow-up.

Because children—particularly those of poor families—are among the major sufferers from lead poisoning, the Cincinnati group has centered its efforts in this area. "In the past," says Dr. Allen, "we have failed rather miserably in improving the environments of children who have been poisoned. A good number of our cases are repeated offenders. After being diagnosed, treated, and 'deleaded,' they are sent home only to return with evidence of further absorption of lead."

In actuality, it is this very pattern of repetitious absorption that convinced Dr. Allen and his fellow workers that concerted community action is necessary if the problem of lead poisoning is to be conquered. The first meeting called by Dr. Allen and an associate, Dr. Hugo D. Smith, attracted enthusiastic representation from all municipal agencies dealing with health, housing, and social service. From this nucleus grew the Lead Information Center.

The Center—in addition to its day-to-day operations—is hard at work on model laws that will prohibit the use of lead-based paints on house interiors, the source of most lead poisonings. Small children will chew or ingest almost anything. This, coupled with the fact that poorer homes are more prone to have flaked or peeling paint, makes it obvious why lead poisoning chooses its victims from among the smaller children of low-income families.

Like all idealists, Dr. Allen dreams of a time when federal laws will forbid the use of lead-base paint on the interior walls of dwellings. Meanwhile, he and other members of the Center advocate:

—Local ordinances compelling property owners to remove lead-base paint in homes where cases of lead poisoning have been detected.

—Labeling of all paints containing more than 1% of lead to indicate their danger if ingested.

One other enemy, less accessible to Dr. Allen and his friends, is the do-it-himself parent who repaints shabby toys and furniture with odds and ends of leftover lead-base paints from the workshop shelf.

The Medical Society— Nearly 2,000 Strong

Physicians in Prince William County, Virginia, several months ago organized the county's first known medical society, partly as a result of the transformation of a once rural area into suburban Washington, D. C. Medical societies are born like this every year, even as others pass out of existence, some through district mergers.

While the exact number of county medical societies varies constantly, a count of 1,929 was made recently by the American Medical Association. Membership may range from very few in a sparsely populated region to over 7,000 in metropolitan areas. Information on what 1,191 of the societies are

Society Notes

Officers in local medical societies often wonder what their counterparts around the United States are doing. A new wealth of information now is available from the A. M. A. Council on Medical Service, which is analyzing its 1959 survey in which nearly two-thirds of the county medical societies answered a long list of questions about their activities.

Societies were studied in six groups, according to size: 328 societies having under 15 members, 446 from 15 to 49 members, 163 from 50 to 99 members, 96 from 100 to 199 members, 51 from 200 to 299 members, and 107 a membership of 300 or more.

doing is available, through tabulation of results of an A. M. A. survey made in 1959.

About three-fourths of the societies report they meet once a month and 823 say their attendance averages over 50% of the membership. The type of program which draws the biggest crowd is a well-known speaker, according to 650 replies. Popularity ratings of other programs are socioeconomic meetings, 254; scientific seminars, 221; social programs, 171; and films, 112 (the total is greater than the number of replies, since more than one top choice was listed in some cases).

Of the groups meeting other than monthly, 6 meet biweekly, 98 bimonthly, 139 quarterly, 41 semiannually, and 85 annually. Most of them are comparatively small. Fewer than 10% of the the replies say attendance is decreasing; the rest say it is either increasing or stable.

The most common committee is one on public relations, existing in two-thirds of the societies. Other committees found in over half the organizations are civil defense, legislation, and public health. One change from the 1957 survey is that there now are more civil defense committees than legislative committees.

Personal Touch Favored

Writing a personal letter is the most frequent means of publicizing society views on legislation. Letters were used by 698 societies, personal contacts by 572, resolutions by 370, and meetings with legislators by 339. A spokesman for the press was appointed by 397 societies, 314 had a press code, and 261 held a meeting with the press.

The existence of 289 committees on aging is indicative of a trend toward increasing interest by local medical groups in this field. Many of the committees still were in the research or study stage. Action programs frequently took the form of cooperation with Golden Age Clubs or similar groups and conferences with nursing home representatives.

In promoting community projects, 331 societies worked with the Chamber of Commerce, 203 with the Junior Chamber of Commerce, 153 with farm organizations, and 71 with the AFL-CIO. Activities in the insurance field were varied; 553 societies had liaison committees with Blue Shield. Grievance committees existed in 707 societies, 18 of the committees handling only fee disputes and 689 all types of disputes.

The reports showed the wide variety of activities in which medical societies participate: 590 of them had an emergency call plan, 199 a collection agency, 72 a bureau of medical economics, 382 some type of fee schedule, 221 a relative value or fee index, 49 a medical foundation, 80 a physicians' placement service, 88 a scholarship program for students, 147 a central society office, 11 a home for physicians and 82 an assistance program for physicians. Training courses for ambulance personnel were conducted by 54 societies, clinics on athletic injuries by 110, and campaigns against food faddism by 60.

Only 107 societies had 300 members or more, while 774 societies had fewer than 50 members.

The Los Angeles County Medical Association, with a membership of 7,553, has become the largest in the nation, overtaking the 7,000-member Medical Society of the County of New York.

Young Minds Are Being Challenged by Physicians

Twenty-one boys and girls watched intently as the speaker explained the intricacies of radiology and its uses in medicine. Many collegians would have been baffled by the details, which were readily absorbed by the group—all high-school sophomores, juniors, and seniors—hand picked for their brains and enthusiasm. The lecturer was a practicing physician, volunteering his spare time for a salary of $1.00 per year and the satisfaction of challenging bright young minds to work at full capacity.

Scenes similar to this are taking place one night a week in 400 communities in the United States. Instead of a physician, the instructor may be a dentist, veterinarian, chemist, agronomist, engineer, mathematician, or social scientist. They, and men from other fields, are taking turns in helping to present a broad view of science to selected students, at an intellectual level which would be impractical in the regular curriculum.

The science seminars have spread in the past two years under sponsorship of the Joe Berg Foundation, established by a midwestern manufacturer impressed with an after-school-hours program in which his grandson was participating in Skokie, Ill. Mr. Berg appointed as foundation coordinator Jacob Shapiro, who had founded the Skokie program. Mr. Shapiro, a former Tennessee school teacher who later entered private business, had a theory that every community has bright youngsters who should be ferreted out and who should receive encouragement beyond what they can get in the normal classroom. Recruiting instructors from offices, laboratories, and industrial plants, he called the key to success in teaching not the completion of courses in educational theory but rather knowledge of a subject and enthusiasm for it.

Many Doctors Active

While the foundation assists with the establishment of a seminar program, each community has planned, directed, and tailored its own to fit the local situation. The youngsters, who may represent only 0.5% of the student body, are selected through a process which includes writing tests and being interviewed together with their parents. The high school group in one California community has heard lectures by three Nobel prize winners.

Physicians and others in the medical field are among the instructors in most of the 400 participating schools, Shapiro has found. At Neodesha, Kan., a town of 3,700 population, the coordinator of the program has been a physician, Dr. C. E. Stevenson, whose special interest is anatomy. Two other instructors at Neodesha are also physicians, Drs. Glen M. McGray and Frank A. Moorhead.

In most communities the night classes, lasting two and one-half hours, are held nearly 52 weeks a year. The series of discussions are kept diversified to give the teen-age participants a general perspective, discouraging them from developing a narrow specialized outlook prematurely. Each student is required to undertake a research project for the year, an activity going far beyond mere hobby craft. In one community, one youth studied animal behavior and reaction to surroundings, another paramecium encystment and excystment, and a third established a bee farm to observe bee communication.

Students are carefully screened and assessed before being allowed to join seminar programs.

View from the Lectern

High-school students may look on a medical career either as hard work or as a rewarding vocation. What advice should be given them by doctors who are asked to speak in a career lecture series? Here is some recent counsel to students:

The practice of medicine is a never-ending voyage of discovery. No amount of money can equal the satisfaction you receive from helping a patient regain his health.—Dr. Walter L. Palmer. Chicago.

A good physician must have a real interest in biological phenomena and kindness, judgment, and empathy.—Dr. H. Sherwood Lawrence, New York.

Contrary to popular notions, a small college often is to be preferred over a large one by the student preparing for medical school. A background in science and mathematics definitely is not a prerequisite; the subject is less important than the fact a person has definite knowledge in some particular field. One medical student had majored in Greek.—Dr. Robert G. Page, Chicago.

Medicine's Friendly Rivals

From astrophysics to zoogeography, hundreds of sciences compete today for talented young minds. Boys who once would readily have turned to medicine as a career may now be contemplating creating new gadgets for the American household or shooting rockets to the stars. The seminars may provide an opportunity for men from different fields, including medicine, to engage in a friendly rivalry.

In few of the science programs is medicine as heavily represented as the one in the Sequoia high school district in California. The project has had the assistance of six physicians: Drs. Donald Rowles, a thoracic surgeon; Glen Haydon, of Stanford University Medical School; Henry Mayer and Elmer Ng, radiologists; Ernest Nelson, a general practitioner with previous training in genetics; and Robert S. Hoyt, a pathologist.

Although two-thirds of the lectures were on subjects outside the life sciences, the physicians and others led discussions on life, concerning definitions, origins, changes due to genetic factors, and the role of viruses and their relationship to mammalian cell physiology.

"Electronics firms in this area," Dr. Hoyt says, "are sending their best engineers and technical experts to stimulate interest among qualified students. . . . It is the responsibility of physicians and biologists to present the truly interesting nature of our field of study. We may find ourselves in 10 to 15 years with relatively few competent people receiving their Ph.D.'s in biology and related sciences."

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THE PHYSICIAN AND THE SCIENCE WRITER

NOT many years ago the physician was as suspicious of the aims of the newspaper reporters as the reporter was scornful of the lack of cooperation usually given by the doctor. Progress has been made during the past decade to bridge the chasm between the two professions. It is anticipated that, as we enter the new decade, the science writer and the physician will continue to pursue their respective goals conjointly, when this is indicated. Each has his professional assignment and neither one should ignore the rights, privileges, and ethics of the other. The public seeks information about contemporary progress in scientific medicine and is as prone to look for such information in the daily press as in consultation with the family doctor.

Liaison between the science writer and the physician is probably better understood by the former, because gathering news and disseminating it is his full-time task. The physician, on the other hand, encounters the press infrequently and enters the press conference under a disadvantage because of limited experience. In selected instances the public relations officer of the county or state medical society is prepared to offer invaluable aid in briefing the physician prior to the conference and lending assistance during the conference. This is probably the most satisfactory procedure in overcoming formidable barriers. One enlightened state medical society has recognized that, in the absence of a representative of the public relations division, it is ethical for the physician, without any intervening mediator, to comply when a request has been extended by a representative of the press, radio, or television for revelation of scientific facts.[1]

The Principles of Medical Ethics was designed to protect the public in the days before radio and television. It should be respected in this concept rather than in the role of censorship of the physician. Glorification of the doctor in order to enhance his practice is not a threat today as it was some years ago. Such fears should not enter into serious thought or procedure of contempory doctor-press liaison.

Some time ago the Josiah Macy, Jr. Foundation sponsored a series of conferences, held at infrequent intervals, between science writers and physicians. The protocol was informal, in keeping with the practice adopted by the officers of the foundation. The conferences were attended by private physicians, without specific representation, physicians who spoke for organized medical societies, and science writers. The pertinent discussions were edited by Kreighbaum and bound in a paperback volume that provides enlightening reading.[2]

One experience is recounted of a well-known physician. This might be applicable in other instances. After an appearance on a statewide television program that reached an estimated 500,000 viewers, digests of the program were sent to about 3,000 on direct request. Not a single person attempted to communicate directly with the doctor for medical care; not a single request was directed to the physician for further information. It was judged that the fear of unfair professional advantage from such publicity had been expanded to an unrealistic size.

The established practice of press conferences in connection with the innumerable medical meetings that are held almost continually throughout the United States has helped tremendously in making scientific information available to the public, without fear by the physician of self-aggrandizement. Undoubtedly the medium is responsible for a significant body of medical news that reaches the public regularly. The press is welcome at most medical meetings, large and small, because the job that is being done to foster better relations between the public and the medical profession needs such cooperation. The press is as anxious and as willing to help as the public is eager to get the latest and most authoritative news.

BRAIN FEVER

The Holmesian enthusiast will rejoice that the term "brain fever" is again in good repute and is accepted by the medical fraternity. The very fact that the staid JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION has published an article bearing the title "Brain Fever" has stripped criticism of all weapons. The loyal Holmesian no longer needs to feel apologetic for the nomenclature of Dr. Watson intended to describe a rather unusual and fortunately rare clinical entity.—E. J. Van Liere, A Doctor Enjoys Sherlock Holmes, New York, Vantage Press, Inc., 1960.

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[1] Guide for Cooperation: For Doctors, Hospitals and Reporters, ed. 2, New York, Medical Society of the State of New York.

[2] When Doctors Meet Reporters, compiled by Hillier Kreighbaum, Josiah Macy, Jr. Foundation, New York, New York University Press, 1957.

ORGANIZATION SECTION

SPECIAL STUDY COMMITTEE

William F. Norwood, Ph.D., has been appointed staff director for the Special Study Committee of the A. M. A. Council on Medical Education and Hospitals. He is on leave from the College of Medical Evangelists, Los Angeles, where he is chairman of the division of legal and cultural medicine. Dr. Norwood has been on the faculty at the College of Medical Evangelists since 1933. From 1950 to 1951 he was on leave of absence to serve as a staff associate in a survey of medical education sponsored by the A. M. A. and the Association of American Medical Colleges. The next year he served as a consultant to the W. K. Kellogg Foundation, Battle Creek, Mich.

The A. M. A.'s House of Delegates authorized the creation of the Special Study Committee in December, with the following objectives: to (1) present a scholarship program for medical students, including the A. M. A.'s role in fulfilling it; (2) ascertain the maximum to which medical schools can expand their student bodies and what universities can support new medical schools, either on a two-year or a four-year basis; and (3) investigate means of securing additional competent medical faculties, financing of expansion and establishment of medical schools, financing of medical education, and relaxation of rigid geographical restrictions on admission of students.

Eleven members of the 12-man Committee have been selected, as follows: representing the House of Delegates, Drs. Charles Hayden, Charles Hudson, and Willard Wright; representing the Board of Trustees, Drs. James Appel, Hugh Hussey, and Julian Price; representing the Council on Medical Education and Hospitals, Drs. Leland McKittrick, Committee Chairman, W. Clarke Wescoe, and John Z. Bowers; and representing the Association of American Medical Colleges, Drs. John McK. Mitchell and William R. Willard. A third representative of the latter group remains to be selected. The House asked for a first report from the Committee at its June meeting.

ACCIDENTAL POISONINGS

The American Medical Association is urging passage of federal legislation requiring precautionary labeling of all hazardous packaged chemicals used for nonmanufacturing purposes which are not now required by law to carry warnings.

The A. M. A.'s Committee on Toxicology drafted a model "hazardous substances bill." A measure containing almost identical language, H. R. 7352, 86th Congress, was introduced in Congress last May. The A. M. A. hopes the measure will be enacted and will serve as a model for similar state laws.

Latest U. S. statistics show that 1,422 persons—355 of them preschool children—died from accidental overexposure to packaged chemicals in one year. In addition to the fatalities, there were about 200,000 nonfatal injuries from accidental poisonings.

As part of its campaign for passage of H. R. 7352, the A. M. A. has prepared a 20-page booklet about the bill and the problems which led to drafting it.

The A. M. A. has also published a card listing poison prevention rules and giving tips on first-aid procedures to use in cases of poisoning. This card, which is designed to be placed inside medicine cabinet doors for quick reference in emergencies, also carries a legislative message encouraging public support of H. R. 7352.

Both pieces can be obtained by writing to the Committee on Toxicology, American Medical Association, 535 N. Dearborn St., Chicago 10.

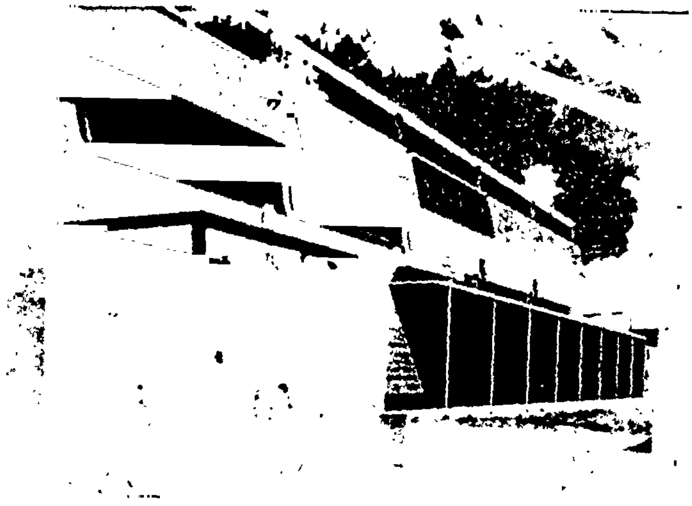
HUMAN DISSECTION

Under Rokitansky human dissection reached incredible proportions. He extracted the procedure to the marrow of its bones. From 1827 to 1866 the master prosector personally performed over 30,000 necropsies! An average of two a day, every day, for 39 years! In addition, he had access to protocols from another 40,000 necropsies done during his tenure. This amazing number was made possible by the fact that permission of the next of kin was not required for necropsy to be performed. Necropsy in the event of death was self-understood upon entering the hospital. The family of the deceased could actually refuse to allow it, and a certain waiting period after death was mandatory for that purpose (as well as to establish beyond doubt the fact of death and to thereby avert dreaded premature burial). However, such refusal could at best be only a token gesture, for the state government was so organized that refusal could easily be overruled by hospital authorities. Consequently, at the Allgemeines Krankenhaus necropsy rates were consistently 100 percent of all deaths, ranging on the average from 1,500 to 1,800 per year. This philosophy and legislation coupled with the exceptional talents of Rokitansky created the optimal conditions for human postmortem dissection to reach its pinnacle.—J. Kevorkian, The Story of Dissection, New York, Philosophical Library, 1959.

MEDICAL NEWS

CALIFORNIA

Dedicate Rehabilitation Institute in Los Angeles.—The principal speakers for dedication of the new one-million-dollar rehabilitation center at Cedars of Lebanon Hospital, Los Angeles, March 31 were Dr. Howard A. Rusk, New York City, director, Institute of Physical Medicine and Rehabilitation, New York University–Bellevue Medical Center, and Dr. Henry H. Kessler, director, Kessler Institute for Physical Rehabilitation, West Orange, N. J. Under construction since September, 1958, the center will provide facilities for treating arthritis, multiple sclerosis, poliomyelitis, and other disabling diseases and accidents. Financed through community support in addition to $405,000 in federal and state Hill-Burton funds, there will be a capacity of 250 patients per day, triple the present daily patient average, according to Dr. John H. Aldes, director of the rehabilitation center. Named for Ben H. Meyer, late president of the Union Bank of Los Angeles and a former president of Cedars, the 20,000 square foot structure has two stories with another floor below ground level and was designed to allow addition of two more stories. The ground floor contains a hydrotherapy section, an orthopedic brace shop, a gymnasium, a resistive exercise room, and 20 patient treatment rooms. On the second floor are an audiospeech therapy section and a children's therapeutic playground. Here also are the rehabilitation library and patients' conference rooms, offices for medical staff, social service, vocational guidance, and psychology counselors. Closed circuit television for diagnostic study and teaching has been installed throughout the building, which is connected to Cedars' main hospital unit by underground tunnel.



The new rehabilitation center at Cedars of Lebanon Hospital, Los Angeles.

Society News.—The Metropolitan Dermatological Society of Los Angeles installed the following officers for 1960: president, Dr. Max Popper, Beverly Hills; vice-president, Dr. Murray Zimmerman, Whittier; secretary-treasurer, Dr. Rose B. Saperstein; and program chairman, Dr. John W. Carney. ——The new officers of the Los Angeles Society of Allergy are: Drs. Isadore Pitesky, Long Beach, president; Catherine R. G. Pearson, Pasadena, vice-president; and Sheldon C. Siegel, secretary-treasurer.

COLORADO

Teenage Venereal Diseases.—The Colorado State Department of Public Health reported that the 10-to-19-year-old age group has consistently accounted for about 20% of all gonorrhea cases reported in the state. In the infectious syphilis cases, however, this group represented a little over 10% of the total. Until last year (1959) they accounted for 22% of all early infectious syphilis cases reported in the state. In 1958 for ages 10-19, there were 11 cases of infectious syphilis reported, or 12.36% of the total for all ages of 89 cases.

Hospital Establishes Lectureship Series.—The National Jewish Hospital at Denver announced the initiation of a visiting lectureship series. The first lecture will be given at 8 p. m., April 18, in the auditorium of the National Rehabilitation Center Building at the hospital. Dr. E. J. Moran Campbell, assistant, The Medical Unit, The Middlesex Hospital, London, England, will present "Diagnosis and Treatment of Respiratory Failure." The second lecture will be given at 8 p. m., May 23, in the auditorium of the National Rehabilitation Center Building, with Dr. Chandler A. Stetson Jr., chairman, department of pathology, New York University College of Medicine, New York City, presenting "Transplantation Immunology."

CONNECTICUT

Study of Driver Health and Accidents.—Connecticut has been chosen by the U. S. Public Health Service for a study to determine whether a relationship exists between the health of motorists and traffic

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Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

Woods Schools, Langhorne, Pa., and the Massachusetts Special Commission on Retarded Children, the conference will be held at the Massachusetts Mental Health Center, 74 Fenwood Road. Discussions will center on "The Outlook for the Adult Retarded." Massachusetts Governor Foster Furcolo; Mr. Louis H. Ravin, of the Special Staff on Aging for the White House Conference, Washington, D. C.; and Dr. Gunnar Dybwad, executive director, National Association for Retarded Children, New York City, will speak at the opening sessions.

NEW YORK

Annual State Report on Health.—The New York State Health Department's annual report, submitted to Governor Nelson A. Rockefeller by Dr. Herman E. Hilleboe, state health commissioner, states that the number of babies born during 1959 in the state reached an all-time high of 363,124, bringing the state population to an estimated 16½ million. Estimates indicate that the number of persons 65 and over is expected to reach about 2 million in 1970, and comprise a record of 10.7% of the total population. The death rate, 10.5 per 1,000, remained the same as for the last three years. Diseases of the heart accounted for 43.8% of all deaths, followed by cancer, 17.6%, and vascular lesions of the central nervous system, 9.1%. The cancer death rate, 185.5 per 100,000 was the second lowest since 1951. Dr. Hilleboe said that since 1950 the tuberculosis death rate has decreased 70%. There were some declines from 1958 in the reported cases of childhood diseases: German measles cases reported to the department dropped from 16,386 to 10,784; measles dropped from 36,006 to 19,578; chickenpox declined from 18,264 to 15,494.

Dental Instruction Via Television.—The first scientific study of the use of closed circuit television for full-scale professional instruction toward a doctoral degree got underway in March at New York University's College of Dentistry. The study will be financed in part by a grant of $155,140 from the U. S. Office of Education. To determine the effectiveness of televised as compared with conventional instruction, the entire sophomore class in operative dentistry will be divided into two sections of 85 students each. The control group will learn by the conventional means—lecturers, blackboard work, demonstrations, slides, and films. The experimental group will study the same material but through the medium of television. Both groups of students will be tested regularly through written and practical examinations, and the results will be evaluated on the basis of previous grades and the results of nationally standardized examinations. At the end of each trimester members of the experimental group will be required to evaluate their television experience in terms of past conventional instruction. The NYU College of Dentistry has used closed circuit television since 1956 in undergraduate and postgraduate courses and for the transmission of special programs to groups outside the college.

pedic surgery, discussing athletic injuries. Elective induction of labor at term will be the topic of a Thursday afternoon address delivered by Dr. Bernard J. Hanley, Los Angeles obstetrician. "Transplantation of the Kidney" by Dr. Clarence V. Hodges, head of the division of urology, will be a feature of the Friday afternoon talks. The Alumni Association's annual banquet Thursday, April 21, in the Sheraton Hotel will be preceded by a social hour, 7 to 8 p. m. and followed by a dance. A three-day sectional meeting of the American College of Surgeons will be held March 28-30 at the Sheraton Hotel in Portland, and elected medical motion pictures and cine clinic films from the 1959 clinical congress will be shown. For information on the reunion, write the University of Oregon Medical School, 3181 S. W. Sam Jackson Park Rd., Portland 1, Ore.

RHODE ISLAND

Superintendent Named for Health Center.—Dr. Charles H. Jones, superintendent of Northern State Hospital, Sedro Woolley, Wash., was appointed superintendent of Butler Health Center, Providence, by the board of trustees. He succeeds Dr. John S. Bockoven, acting superintendent, who has accepted the post of superintendent of the Cushing State Hospital at Framingham, Mass. Dr. Jones, a 1943 graduate of the University of Oregon Medical School, Portland, entered state hospital service in Washington in 1946 and was appointed superintendent of Northern State Hospital in 1950.

TENNESSEE

Symposium on Radioactivity.—The section on medical sciences of the American Association for the Advancement of Science in sponsoring a Symposium on Radioactivity in Man, Measurements and Effects of Internal Gamma Ray Emitting Radioisotopes, to be held at Vanderbilt University, Nashville, April 18-19. The conference is made possible by a grant from the United States Steel Foundation to the association and is supported in part by the Division of Biology and Medicine of the Atomic Energy Commission, the Public Health Service, and the Army Medical Research and Development Command. Twenty-four papers are scheduled, with discussions to follow each group of three papers. Speaker at the dinner April 18, will be Mr. J. B. Austin, administrative vice-president, Research and Technology, United States Steel Corporation, Pittsburgh, presenting "Public Relations for Scientists." A panel discussion April 19, 2:30 p. m., will conclude the meeting. For information, write the Symposium Chairman, Dr. George R. Meneely, School of Medicine, Vanderbilt University, Nashville 5, Tenn.

TEXAS

Annual Symposium on Nuclear Medicine.—The third annual Symposium on Nuclear Medicine sponsored by the Committee on Nuclear Medicine of the Texas Medical Association will be held April 9 in Fort Worth. The morning sessions will include a tour of Convair nuclear facilities, headed by Dr. J. K. Leverett, chief physician, Convair Fort Worth Division, General Dynamics Corporation. The afternoon session will include a symposium, "Medical Significance of Fallout and Problems of Radioactive Waste Disposal," at which the following papers will be presented:

Fallout—Is It a Hazard to Man?, Wright H. Langham, Ph.D., Los Alamos, N. M.
Radioactive Fallout on Marshallese and Japanese Fishermen—Five Year Follow-up, Dr. James S. Robertson, Upton, N. Y.
Problems Arising from Fallout from a Russian Nuclear Detonation on Berkeley, California—March 1958, Hardin B. Jones, Ph.D., Berkeley, Calif.
The Problem of Radioactive Waste—Present and Future, Mr. Joseph A. Lieberman, Washington, D. C.
Problems Associated with Disposal of High-Level Radioactive Wastes in Deep Geologic Formations—Natural Salt Formations, William B. Heroy, Ph.D., Dallas, Texas.
Radioactive Liquid Waste at Convair, Division of General Dynamics, Fort Worth, Texas, Mr. Frank Paschal, health physics department, Convair, Fort Worth, Texas.

Two special exhibits have been prepared for the symposium. For information, write Dr. Herbert C. Allen Jr., Chairman, Committee on Nuclear Medicine, Texas Medical Association, 1801 N. Lamar Blvd., Austin, Texas.

VERMONT

Dr. Melville Named Department Chairman.—Prof. Donald B. Melville was appointed chairman of the department of biochemistry, University of Vermont College of Medicine, Burlington, effective July 1. Dr. Melville, associate professor of biochemistry, Cornell University Medical College, New York City, will succeed Harold B. Pierce, Ph.D., retiring department chairman. A graduate of the University of Illinois, Dr. Melville served for three years as a teaching assistant and university fellow there. He joined the faculty of the Cornell Medical College as a research associate in 1939.

WISCONSIN

Dr. Akert Honored by Swiss Society.—The Swiss Academy of Medical Sciences announced recently that Dr. Konrad Akert, University of Wisconsin associate professor of anatomy, has been awarded the Robert Bing Award in Neurological Sciences. He will share the award, given for "distinguished research," with Prof. P. Buser, of Paris, France. In June, Dr. Akert will deliver a lecture in Basle, Switzerland, and receive the award's stipend, about $4,000. Dr. Akert was born in Zurich, Switzerland,

and received his M.D. from the University of Zurich in 1946. In 1953, Dr. Akert joined the Wisconsin faculty as assistant professor of physiology. He was named associate professor in 1955.

University News.—Dr. Jerzy E. Rose, associate professor of physiology and psychiatry, Johns Hopkins University School of Medicine, Baltimore, will come to Wisconsin as professor of neurophysiology July 1, joining the staff of the laboratory of neurophysiology, department of physiology, in the new Medical Sciences Building. He succeeds Dr. Konrad Akert, who recently was appointed professor of neuroanatomy in the department of anatomy.—Charles W. Cotterman, Ph.D., has been appointed professor of medical genetics at the University of Wisconsin Medical Center and assumed his duties on Feb. 1. Dr. Cotterman has been professor of genetics and biometry, Graduate Research Institute of Baylor University, Houston, Texas.

GENERAL

Tuberculosis in Nigeria.—Western Nigeria's "Chest Clinic" has treated more than 3,500 tuberculosis patients since it was opened in Ibadan in October, 1958, Dr. H. M. Sultana, the clinic's chief medical officer, reported. Of this number, 1,000 patients have completed their treatment and the rest are in various stages of recovery. Dr. Sultana said that six of every 1,000 persons in Ibadan had tuberculosis in 1957, according to a survey conducted by the World Health Organization. The Ibadan Chest Clinic includes a 20-bed ward which was opened in March, 1959, for treatment of in-patients.

Meeting of Physicians in San Francisco.—The 41st annual session of the American College of Physicians will be held in San Francisco April 4-8, with general headquarters at the Civic Auditorium. Dr. Howard P. Lewis, Portland, Ore., president of the college, will preside at the opening scientific session the afternoon of April 4. Over 100 papers are scheduled for presentation. The John Phillips Memorial Lecture, "Pulmonary Emphysema; New Patterns in an Old Disease," will be given by Dr. Dickinson W. Richards, New York City. The Lilly Lecture will be given by Dr. Alberto Hurtado, Lima, Peru, entitled "Clinical Aspects of Life at High Altitudes." Basic scientific and clinical pathological conferences will be held April 5-8 on the biology of viruses, psychopharmacology, gastric problem, vascular problem, pulmonary problem, and intestinal problem. Hospital clinics will be conducted April 5-7. Twenty panel discussions, a program of colored television presentations, and technical exhibits are planned. The annual banquet will be held April 7, 8 p. m. A program of ladies' activities is arranged, and a postconvention tour to Hawaii will begin the morning of April 9. For information, write the American College of Physicians, 4200 Pine St., Philadelphia 4.

Manual for Planning Pediatric Service.—For communities planning to build a hospital, the American Academy of Pediatrics has published a manual of information, "Care of Children in Hospitals." Keyed to problems of the average American community where the prime consideration is service to patients, the book offers suggestions for hospital construction, and the organization and operation of a pediatric service, Dr. E. H. Christopherson, Evanston, Ill., executive director, said. The manual was written by the academy's Committee on Hospital Care with the advice of medical and architectural consultants, the United States Public Health Service, the American Hospital Association, American Public Health Association, National League for Nursing, American Medical Association, and the Children's Bureau. It was published through a grant from Pet Milk Company. The manual contains chapters on the general hospital's responsibility for child care, a pediatric service, plans for the pediatric unit, childhood surgery, communicable disease techniques, meeting the emotional needs of the hospitalized child and adolescent, laboratory service, child feeding, education, and training. For information, write the American Academy of Pediatrics, 1801 Hinman Ave., Evanston, Ill.

Conference on Microcirculation.—The eighth Microcirculatory Conference will be held April 12 at the Statler-Hilton Hotel, New York City. Dr. John W. Irwin, of the Massachusetts Eye and Ear Infirmary, Boston, chairman of the conference, will open the program with welcoming remarks. The program is as follows:

Circulation of the Pituitary
  General and Comparative Aspects of Pituitary Circulation, Dr. John D. Green, Los Angeles.
  Relationships of Pituitary Vasculature to Physiology of the Pars Distalis, John W. Everett, Ph.D., Durham, N. C.
  Studies on the Small Blood Vessels of the Living Pituitary, Dr. W. Curtis Worthington Jr., Charleston, S. C.
  Electron Microscopic Studies of the Capillaries of the Anterior Pituitary Gland, Marilyn G. Farquhar, Ph.D., New York City.
Circulation of Bone Marrow
  Experimental Investigation of Microcirculation in Bone Marrow, P-I Branemark, Lund, Sweden.
  Electron Microscopic Study of the Vascular Bed of Bone Marrow, L. M. Zamboni and Daniel C. Pease, Ph.D., Los Angeles.
  The Effect of Environment on Proliferation and Maturation of Nucleated Red Cells, Dr. Allan J. Erslev, Philadelphia.

A business meeting is planned for 4 p. m. For information, write Herbert J. Berman, Ph.D., Department of Biology, Boston University, Boston 15, Secretary-Treasurer.

U. S.-Canadian Commission on Alcoholism.—A new international (U. S.-Canadian) commission has been organized and a million-dollar U. S. government grant has been authorized to review what is known about alcoholism, to review what is being done in treatment, education, and research, and to seek answers to the question as to what had better be done concerning alcoholism over the next 20 years or so. The work of the commission, under a scientific director yet to be named, who is in turn responsible to a 25-man body of scientists and laymen, is to extend over a five-year period. Although the commission will be an independent body, most of the work will be centered in a major American University. In addition, "task forces" which will deal with various aspects of the problem may be located at any suitable place in the United States or Canada. Scientific knowledge of alcoholism as a disease and as a social problem will be examined and reevaluated. The whole structure of organizations which deal with alcoholism or bear on it in any way will be brought under fresh study. Members of the new cooperative commission will be appointed by an interim commission (already in existence under the chairmanship of H. David Archibald, Toronto, president, North American Association of Alcoholism Programs. For information, write Mr. Archibald at 9 Bedford Rd., Toronto 5, Ontario, Canada.

Awards for Medical Monographs.—The editors of "Modern Medical Monographs" announced the 1960 competition for unpublished manuscripts on clinical subjects in internal medicine. The purpose of these annual Modern Medical Monographs Awards is to "stimulate young physicians to communicate their work in the classical form of the monograph and to achieve high standards of medical writing." The first prize is $500. The authors of other top-ranking suitable manuscripts will be offered a contract for publication of their work as a book in the series, "Modern Medical Monographs," under standard royalty arrangements. Entries will be judged for style and clarity of expression by a committee of the American Medical Writers' Association, and for clinical interest and scientific value by the editors and advisory board of the monograph series. Rules are as follows: (1) the author must be a graduate physician, less than 40 years of age; (2) manuscripts (including illustrations, if any) should be submitted in duplicate by registered mail, postmarked no later than Dec. 1, to Dr. Irving S. Wright, 450 E. 69th St., New York 21; (3) the manuscript, including the bibliography, must consist of not less than 130, or more than 200, double-spaced typewritten pages with one-inch margins, and not more than 30 illustrations (pictorial charts, drawings, diagrams, or photographs); (4) Dr. Morris Fishbein's book, "Medical Writing" (third edition), should be followed in preparation of the manuscript, use of abbreviations, etc., and bibliographic form.

Experimental Biology Meeting in Chicago.—The 44th annual meeting of the Federation of American Societies for Experimental Biology will be held in Chicago April 11-15, with headquarters at the Conrad Hilton Hotel. The federation includes the American Physiological Society, American Society of Biological Chemists, American Society for Pharmacology and Experimental Therapeutics, American Society for Experimental Pathology, American Institute of Nutrition, and American Association of Immunologists. A joint session is planned for the evening of April 12 on the theme "Pharmacological Aspects of Current Social Problems." Special sessions on physiology, biochemistry, nutrition, and immunology are planned, and intersociety sessions will include the following symposiums:

Radiation Protection and Recovery.
Animal Behavior and Neurophysiological Correlates.
Gastroenterology.
Problems in Toxicology I.
Problems in Toxicology II.
Current Concepts in Lipid Metabolism.
New and Neglected Hormones.

A motion picture session will be held April 11, 8 p. m. Industrial scientific exhibits are planned, and special meetings, dinners, luncheons, and group breakfasts are scheduled. The American Society for Artificial Internal Organs will hold scientific sessions April 10-11 at the Congress Hotel, and federation members may attend. For information, write the Federation of American Societies for Experimental Biology, % Milton O. Lee, Ph.D., 9650 Wisconsin Ave., Washington, D. C.

Awards for Heart Studies.—The American Heart Association on Feb. 24 announced the award of a record $1,812,885 to 176 scientists for research covering basic and applied studies in the field of heart and blood vessel diseases. The awards, effective July 1, were announced by Dr. A. Carlton Ernstene, president of the association, who pointed out that they were made possible by voluntary public contributions to the annual Heart Fund appeal. The awards provide for continued support of the association's seven "Career Investigators," scientists selected to receive support throughout their productive lives. The 176 scientists will pursue their studies in 28 states, the District of Columbia, and four foreign countries. Included were 96 "Established Investigators." This category provides five years of uninterrupted support to "highly qualified" scientists conducting independent programs of research. The awards named 44 "Advanced Research Fellows" and 29 "Research Fellows." Usually given for two years, both of these fellowships enable younger scientists to obtain training in research methods under experienced guidance. The awards included departmental grants to the institutions in which all established investigators and advanced research fellows will work. The new fellowship awards represent the first part of the 1960-1961 national research support program in which the association's national office participates jointly with its state and local affiliates. Another group of national awards, in the grant-in-aid category, will be announced in the near future. Research awards also will be made directly to scientists by local heart associations for studies in their own areas as well as throughout the country.

Simplify Quarantine at International Airports.—The U. S. Public Health Service announced the adoption of simplified quarantine procedures at international airports. The principal change is elimination of group clearance, which preceded individual quarantine clearance on arrival of planes from foreign countries. Under the new procedures, if the aircraft captain certifies that no illness has been observed during flight, only individual clearance of passengers is required. Group clearance had been maintained to prevent spread of disease by travelers who might have symptoms of quarantinable illness on arrival. If such illness is reported aboard a plane, or there is an unusual disease problem in the country where the flight originates, the "strictest" quarantine procedures will be applied. The only major airport where passengers will be kept in groups is Miami, Fla., where the means of access to quarantine facilities make the change impractical. The new procedures stress the responsibility of travelers for maintaining valid immunization records and the responsibility of airlines for reporting illness observed among passengers. The quarantinable diseases defined by international sanitary regulations are smallpox, yellow fever, cholera, plague, louse-borne typhus, and louse-borne relapsing fever. None of the quarantinable diseases is known to have been introduced into the United States from foreign countries since a smallpox outbreak in the New York City area in 1947, although quarantinable disease continues to occur in other parts of the world. Both citizens and aliens entering the United States (except persons coming from exempt areas) must have an international certificate of smallpox vaccination, received within three years of arrival. Persons who have recently been in an infected area, may be detained for medical observation for a period up to 14 days. Information on vaccination requirements and recommendations may be obtained from Public Health Service Publication No. 384 (revised 1959), "Immunization Information for International Travel," for sale by Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 30 cents.

FOREIGN

Conference on Poliomyelitis in Copenhagen.—On July 26-28 in Copenhagen, Denmark, the fifth International Poliomyelitis Conference will be held under the sponsorship of the National Foundation and the Danish Infantile Paralysis Association. The general chairman of this conference is Dr. E. Juel Henningsen, deputy minister of health of Denmark. The honorary presidents of the conference are Dr. Jacob Orskov, of Copenhagen, and Mr. Basil O'Connor, of New York City. The meetings will take place at the Falkonercentret, Copenhagen, and the official hotel will be the Hotel 3 Falke. The opening section will deal with over-all viruses of 1960. The second section will be a discussion of the present status of the killed or inactivated virus vaccines which will include "Efficacy," "Duration of Immunity," "Standardization of Potency," and "Recent Developments." This section will be under the leadership of Prof. Stuart Harris, Royal Hospital, Sheffield, England. The third section will deal with all the aspects of the live attenuated virus vaccine and will be divided into three sessions, with a special panel of investigators concerned with the production of attenuated vaccines, representing the U. S., Russia, Czechoslovakia, Holland, Poland, Costa Rica, and the Belgian Congo at the third session. Dr. Frank L. Horsfall Jr., president of Sloan-Kettering Institute, New York City, will summarize the conference. Information may be obtained by writing to Mr. Stanley E. Henwood, Executive Secretary, International Poliomyelitis Congress, 120 Broadway, New York 5.

CORRECTION

Dr. John A. Rush Is Not Dead.—Through a records' error, an obituary was published in the Dec. 19 issue of THE JOURNAL on Dr. John A. Rush. A recent victim of poliomyelitis, Dr. Rush, who lives in Miami, Fla., is not dead.

EXAMINATIONS AND LICENSURE

EDUCATIONAL COUNCIL FOR FOREIGN MEDICAL GRADUATES, INC.

Educational Council for Foreign Medical Graduates: Stations around the world. Sept. 21, 1960. Exec. Director, Dr. Dean F. Smiley, 1710 Orrington Ave., Evanston, Ill.

NATIONAL BOARD OF MEDICAL EXAMINERS

National Board of Medical Examiners: Part I, Various Cities, June 21-22 and Sept. 7-8. Part II, Various Cities, April 26-27. Applications must be received at least six weeks before the date of the examination. Exec. Sec., Dr. John P. Hubbard, 133 South 36th St., Philadelphia.

BOARDS OF MEDICAL EXAMINERS

Alabama: *Examination.* Montgomery, June 21-23. Sec., Dr. D. G. Gill, State Office Bldg., Montgomery.

Alaska:* On application in Anchorage or Fairbanks. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

Arkansas:* *Examination and Reciprocity.* Little Rock, June 9-10 Sec., Dr. Joe Verser, Harrisburg.

California: *Written.* San Francisco, June 20-23; Los Angeles, Aug. 22-25 and Sacramento, Oct. 17-20. *Oral and Clinical.* Los Angeles, San Francisco, June 19; Los Angeles, Aug. 21, and Los Angeles, Nov. 29. *Oral for Reciprocity Applicants.* San Francisco, June 18; Los Angeles, Aug. 20 and Nov. 19. Sec., Dr. Louis E. Jones, Room 536, 1020 N Street, Sacramento.

Canal Zone: On Application. Acting Sec., Dr. B. K. Levin, Health Bureau, Balboa Heights.

Colorado:* *Reciprocity.* Denver, April 12. *Examination.* Denver, June 14-15. Sec., Dr. John B. Farley, 1612 Tremont Place, Denver 2.

Delaware: *Examination and Endorsement.* Dover, June 12-14 and July 21. Sec., Dr. Joseph S. McDaniel, Professional Bldg., Dover.

District of Columbia:* *Examination.* Washington, June 13-14. Deputy Director, Mr. Paul Foley, Department of Occupations and Professions, 1740 Massachusetts Ave., N.W., Washington 6.

Florida:* *Examination.* Miami Beach, June 19-21. Sec., Dr. Homer L. Pearson, 901 N.W. 17th St., Miami 36.

Georgia: *Examination and Reciprocity.* Atlanta, June. Sec., Mr. Cecil L. Clifton, 224 State Capitol, Atlanta 3.

Guam: *Subject to Call.* Act Sec., Dr. F. L. Conklin, Agana.

Idaho: *Examination and Endorsement.* Boise, July 11-13. Exec. Sec., Mr. Armand L. Bird, 304 Sonna Bldg., Boise.

Indiana: *Examination.* Indianapolis, June 22-24. *Reciprocity.* Indianapolis, fourth Wednesday of each month. Ex. Sec., Miss Ruth V. Kirk, 538 K. of P. Bldg., Indianapolis.

Kentucky: *Examination.* Louisville, June 6-7. Sec., Dr. Russell E. Teague, 620 South Third St., Louisville 2.

Louisiana: *Examination and Reciprocity.* New Orleans. June 9-11. Sec., Dr. Edwin H. Lawson, 930 Hibernia Bank Bldg., New Orleans 12.

Maryland: *Examination.* Baltimore, June 15-18. Sec., Dr. Frank K. Morris, 1215 Cathedral St., Baltimore 1.

Michigan:* *Examination.* Ann Arbor and Detroit, June 6-8. Sec., Dr. E. C. Swanson, 118 Stevens T Mason Bldg., Lansing.

Mississippi: *Examination.* Jackson, June. Sec., Dr. A. L. Gray, Old Capitol, Jackson 13.

Missouri: *Examination.* St. Louis, May 27-28. Exec. Sec.. Mr. John A. Hailey, State Capitol Bldg., P. O. Box 4, Jefferson City.

Montana: *Examination and Reciprocity.* Helena, April 5. Sec., Dr. Thomas L. Hawkins, 555 Fuller Ave., Helena.

Nebraska:* *Examination.* Omaha, June 13-15, 1960. Dir., Bureau of Examining Boards, Room 1009, State Capitol Bldg., Lincoln 9.

New Mexico:* *Examination and Reciprocity.* Santa Fe, May 16-17. Sec., Dr. R. C. Derbyshire, 227 East Palace Ave., Santa Fe.

New York: *Examination.* Albany, Buffalo, New York City, Rochester and Syracuse, June 28-July 1. Sec., Dr. Stiles D. Ezell, 23 S. Pearl Street, Albany.

North Carolina: *Endorsement.* Raleigh, May 9. *Examination and Endorsement.* Raleigh, June 20-23. Sec., Dr. Joseph J. Combs, 716 Professional Bldg., Raleigh.

North Dakota: *Examination and Reciprocity.* Grand Forks, July 6-9. Sec., Dr. C. J. Glaspel, Grafton.

Ohio: *Reciprocity.* Columbus, April 5 and June 17. *Examination.* Columbus, June 16-18. Sec., Dr. H. M. Platter, 21 West Broad St., Columbus 15.

Oklahoma:* *Examination and Endorsement.* Oklahoma City, May 31-June 1. Sec., Dr. E. F. Lester, 813 Braniff Bldg., Oklahoma City.

Oregon:* *Reciprocity and Endorsement.* Portland, April 14-16. *Examination.* Portland, July. Exec. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland.

Pennsylvania: *Examination.* Philadelphia and Pittsburgh, July 5-7. Sec., Mrs. Margaret G. Steiner, Box 911, Harrisburg.

Rhode Island:* *Examination.* Providence, April 7-8. Administrator of Professional Regulations, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

South Carolina: *Endorsement.* Myrtle Beach, May 17. *Examination.* Columbia, June 28-29. Sec., Dr. Harold E. Jervey, Jr., 1329 Blanding St., Columbia.

Texas:* *Examination and Reciprocity.* Fort Worth, June 20-22. Sec., Dr. M. H. Crabb, 1714 Medical Arts Bldg., Fort Worth 2.

Utah: *Examination.* Salt Lake City, July 6-8. Director, Mr. Frank E. Lees, 324 State Office Bldg., Salt Lake City 1.

Vermont: *Examination and Reciprocity.* Burlington, June 16-18. Sec., Dr. F. J. Lawliss, Richford.

Virgin Islands: *Examination.* Charlotte Amalie, St. Thomas, June 8-9. Sec., Dr. Benjamin A. Nath, Charlotte Amalie, St. Thomas.

Virginia: *Examination and Reciprocity.* Richmond, June 13-17. Address: Board of Medical Examiners, 631 First St. S.W., Roanoke.

West Virginia: *Examination and Reciprocity.* Charleston, April 18. Sec., Dr. Newman H. Dyer, State Office Bldg. No. 3, Charleston 5.

Wyoming: *Examination and Reciprocity.* Cheyenne, June 6. Acting Sec., Dr. Carleton D. Anton, State Office Bldg., Cheyenne.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

Arkansas: *Examination.* Little Rock, April 21-22. Sec., Dr. A. W. Ford, Department of Education, Education Bldg., Little Rock.

District of Columbia: *Examination.* Washington, May 23-24. Deputy Director, Mr. Paul Foley, Department of Occupations and Professions, 1740 Massachusetts Ave., Washington 6.

Florida: *Examination.* Miami, June 4. Sec., Mr. M. W. Emmel, Box 340, Gainesville.

Iowa: *Examination and Reciprocity.* Des Moines, April 12. Sec., Mr. Elmer W. Hertel, Wartburg College, Waverly.

Kansas: *Examination.* Kansas City, June 10-12. Sec., Dr. Leon C. Heckert, Kansas State College, Pittsburg.

Minnesota: *Examination.* Minneapolis, April 5-6. Sec., Dr. Raymond N. Bieter, 165 Millard Hall, University of Minnesota, Minneapolis.

Nebraska: *Examination.* Omaha, May 3-4. Sec., Mr. R. K. Kirkman, Room 1009, State Capitol Bldg., Lincoln 9.

Oklahoma: *Examination.* Oklahoma City, April 15-16. Exec. Sec., Mrs. E. L. Haidek, 813 Braniff Bldg., Oklahoma City.

South Dakota: *Examination and Reciprocity.* Vermillion, June 10-11. Sec., Dr. Gregg M. Evans, 310 E. 15th St., Yankton.

Texas: *Examination.* Austin, Houston and Galveston, April 8-9. Sec., Dr. Cornelia M. Smith, State Office Bldg., 201 East 14th St., Austin.

Washington: *Examination.* Seattle, July 13-14. Administrator, Mr. Thomas A. Carter, Department of Licenses, Capitol Bldg., Olympia.

Wisconsin: *Examination.* Madison, April 9. Milwaukee, June 4. Sec., Dr. W. H. Barber, 621 Ransom St., Ripon.

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*Basic Science Certificate required.

DEATHS

Adams, John Dresser Ⓜ Boston; born in Boston June 6, 1876; Harvard Medical School, Boston, 1902; specialist certified by the American Board of Orthopaedic Surgery; member of the American Orthopaedic Association and the American Academy of Orthopaedic Surgeons; fellow of the American College of Surgeons; clinical professor emeritus at Tufts University School of Medicine; consultant, New England Medical Center, Boston, Beverly (Mass.) Hospital, Jordan Hospital, Plymouth, Lawrence (Mass.) General Hospital, Melrose (Mass.) Hospital, and the Memorial Hospital in Brattleboro, Vt.; died in the Beverly (Mass.) Hospital Jan. 16, aged 83.

Adkins, George Eli Ⓜ Jackson, Miss.; University of Louisville (Ky.) Medical Department, 1908; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; associated with the St. Dominic–Jackson Memorial Hospital; died Jan. 13, aged 78, of cerebral hemorrhage.

Ainsworth, John B. Ⓜ Raymond, Miss.; Mississippi Medical College, Meridian, 1910; died Jan. 14, aged 76.

Akimoto, Kensuke, Menlo Park, Calif.; Nagoya Medical College, Japan, 1907; died in Tokyo, Japan, Nov. 30, aged 78.

Albano, Galileo, Chicago; Universita di Napoli Facolta di Medicina e Chirurgia, Italy, 1907; on the staff of the Norwegian American Hospital; died in St. Elizabeth Hospital Jan. 29, aged 77.

Arzt, Philip G. Ⓜ Jamestown, N. D.; University of Minnesota College of Medicine and Surgery, Minneapolis, 1905; past-president of the North Dakota State Medical Association; served as president of the state board of medical examiners; fellow of the American College of Surgeons; a director and vice-president of the Jamestown National Bank; member of the Jamestown Park Board since 1931 and its president since 1948; division surgeon of the Northern Pacific and Midland Continental railroads; for many years chief of staff of Trinity Hospital, where he died Jan. 14, aged 78.

Auerbach, Frederick F. Ⓜ Irvington, N. J.; Medizinische Fakultät der Universität, Vienna, Austria, 1923; Deutsche Universität Medizinische Fakultät, Prague, Czechoslovakia, 1932; member of the American Academy of General Practice; associated with the Irvington General Hospital; affiliated with St. James Hospital and Beth Israel Hospital in Newark, where he died Jan. 10, aged 62.

Barnes, DeWitt Roland S., Astoria, N. Y.; McGill University Faculty of Medicine, Montreal, Que., Canada, 1925; died in the Bird S. Coler Memorial Hospital, New York City, Jan. 6, aged 59.

Blesse, Henry Steven Ⓜ Colonel, U. S. Army, retired, Leavenworth, Kan.; Chicago College of Medicine and Surgery, 1916; retired from the U. S. Army Aug. 31, 1951; fellow of the American College of Surgeons; died Dec. 29, aged 69, of cancer.

Bliss, Edward Lydston, Newton, Mass.; Yale University School of Medicine, New Haven, 1891; a medical missionary in China for many years and served under the American Board of Foreign Missions; died Jan. 22, aged 94.

Brown, Victor Emanuel Ⓜ Williamston, N. C.; Syracuse University College of Medicine, 1935; owner of the Brown Community Hospital; died Jan. 15, aged 52.

Castrop, Charles William Ⓜ Dearborn, Mich.; Detroit College of Medicine and Surgery, 1931; member of the American Academy of General Practice; for many years associated with the Dearborn Medical Centre Hospital, where he died Jan. 7, aged 52.

Cattermole, Charles A., San Diego, Calif.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1898; died in El Cajon Jan. 11, aged 89.

Cohen, Bernard Louis Ⓜ Chicago; Chicago Medical School, 1937; veteran of World War II; police surgeon; died in the South Shore Hospital Feb. 4, aged 49.

Dannreuther, Walter Taylor Ⓜ New York City; born in Buffalo May 27, 1885; Long Island College Hospital, Brooklyn, 1906; for many years professor and chairman of the department of obstetrics and gynecology of the New York University Post-Graduate Medical School, where he was professor emeritus of obstetrics and gynecology; chairman, Section on Obstetrics and Gynecology, American Medical Association, 1941-1942; past-president of the American Association of Obstetricians and Gynecologists, American Gynecological Society, New York Medico-Surgical Society and the Medical Society of the County of New York; fellow of the American College of Surgeons, of which he was an ex-governor; for many years president of the American Board of Obstetrics and Gynecology;

Ⓜ Indicates Member of the American Medical Association.

consultant, New York Infirmary, Mother Cabrini, University, Beth David, and Lutheran hospitals in New York City, Wyckoff Heights Hospital in Brooklyn, North Hudson Hospital in Weehawken, N. J., Jamaica (N. Y.) Hospital, Elizabeth A. Horton Memorial Hospital, Middletown, Flushing (N. Y.) Hospital, Fitkin Memorial Hospital in Neptune, N. J., and St. Clare's Hospital, where he died Jan. 27, aged 74, of cerebrovascular disease.

David, John Joseph Ⓜ Springfield, Mass.; Tulane University School of Medicine, New Orleans, 1948; interned at Walter Reed General Hospital in Washington, D. C.; served a residency at the Veterans Administration Hospital in Boston; member of the American Academy of General Practice; served in the medical reserve corps of the U. S. Army; certified by the National Board of Medical Examiners; associated with the Springfield Hospital and the Wesson Memorial Hospital, where he died Jan. 10, aged 36, of injuries received when he was struck by an automobile.

De Courcy, Joseph Luke Ⓜ Cincinnati; University of Cincinnati College of Medicine, 1913; fellow of the International College of Surgeons and the American College of Surgeons; chief surgeon at Good Samaritan Hospital; associated with St. Elizabeth Hospital, Covington, Ky., St. Mary's, Deaconess, and St. Frances hospitals; died Jan. 20, aged 69.

Denison, Lee L., Lake Fork, Ill.; Louisville (Ky.) Medical College, 1897; died Jan. 9, aged 91.

Denney, George Herbert, Wynnewood, Pa.; Medico-Chirurgical College of Philadelphia, 1902; died Dec. 24, aged 82.

Ealy, John Taylor Ⓜ Lancaster, Calif.; born in Gapsville, Pa., Oct. 7, 1917; Temple University School of Medicine, Philadelphia, 1941; interned at the Temple University Hospital in Philadelphia, where he served a residency; served a residency at the Shriners' Hospital for Crippled Children in Philadelphia; specialist certified by the American Board of Orthopaedic Surgery; member of the American Academy of Orthopaedic Surgeons; from 1951 to 1954 on the faculty of Hahnemann Medical College and Hospital of Philadelphia; veteran of World War II; formerly associated with the St. Luke's and St. Joseph's hospitals, and the Children's Medical Center in Philadelphia; died Jan. 18, aged 42, of injuries received in a private plane crash.

Ensminger, Samuel Hyson Ⓜ York, Pa.; Jefferson Medical College of Philadelphia, 1912; died Jan. 8, aged 74.

Fischer, Clarence George Ⓜ Peoria, Ill.; Rush Medical College, Chicago, 1920; interned at the Presbyterian Hospital in Chicago, where he served a residency at the Cook County Hospital; veteran of World War I; member and past-president of the staff of St. Francis Hospital, where he died Jan. 18, aged 67.

Frederich, William John Ⓜ Los Angeles; Rush Medical College, Chicago, 1928; died Dec. 24, aged 63.

Frenkel, Lance Joseph Ⓜ Helmuth, N. Y.; Magyar Kiralyi Erzsebet Tudomanyegyetem Orvostudomanyi, Pecs, Hungary, 1935; served a residency at the Park Avenue Hospital in Rochester, N. Y.; member of the American Psychiatric Association; associated with the Gowanda State Hospital; died Jan. 17, aged 56.

Glenn, George Mills, Fonda, N. Y.; Albany (N. Y.) Medical College, 1911; died Jan. 9, aged 75.

Goodman, Arthur Ouchterlony, Louisville, Ky.; University of Louisville School of Medicine, 1915; the Kentucky Academy of General Practice named him "Family Doctor of 1956"; formerly on the faculty of his alma mater; veteran of World War I; on the staffs of St. Mary's Hospital and the Jewish Hospital, where he died Jan. 16, aged 70, of coronary disease.

Hall, Joseph Andrew, Sierra Madre, Calif.; Manitoba Medical College, Winnipeg, Man., Canada, 1896; served as medical missionary in the Philippine Islands; also an ordained Presbyterian minister; died in Duarte Jan. 14, aged 92.

Harvey, John Woods Ⓜ St. Johnsbury, Vt.; Boston University School of Medicine, 1917; veteran of World War I; formerly practiced in Bayonne, N. J., where he was associated with the Bayonne Hospital; died Jan. 15, aged 75.

Hedgecock, Frederick Monroe Ⓜ Poughkeepsie, N. Y.; St. Louis University School of Medicine, 1930; fellow of the American College of Surgeons; associated with the Vassar Brothers Hospital, where he served as secretary of the staff, and where he died Jan. 16, aged 56.

Hogan, Otto Frederic, Greeleyville, S. C.; Medical College of South Carolina, Charleston, 1916; died in the Kelley Memorial Hospital in Kingstree Jan. 13, aged 68.

Humphrey, Ira Karr, Cordova, Ill.; Rush Medical College, Chicago, 1906; veteran of World War I; died in the Lutheran Hospital, Moline, Jan. 14, aged 77, of malignant prostate.

Hutchinson, Barzilla Milton, Mishawaka, Ind.; College of Physicians and Surgeons, Boston, 1909; the Hahnemann Medical College and Hospital, Chicago, 1912; died Jan. 7, aged 73.

Jones, Leonard Warburton Ⓜ Rochester, N. Y.; Queen's University Faculty of Medicine, Kingston, Ont., Canada, 1902; specialist certified by the American Board of Ophthalmology; member of the

American Academy of Ophthalmology and Otolaryngology; for many years associated with the Eastman Kodak Company medical department; on the staffs of St. Mary's Hospital and Rochester General Hospital, where he died Jan. 13, aged 80.

Karkeet, Robert Budd Ⓜ Portland, Ore.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1909; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; associate clinical professor of otology, rhinology, and laryngology, University of Oregon Medical School; on the staff of St. Vincent's Hospital; died Jan. 22, aged 75.

Koeckert, Herbert Leroy, Cleveland; Western Reserve University School of Medicine, Cleveland, 1918; veteran of World Wars I and II; died in the Lakeside Hospital Jan. 4, aged 66, of cancer of the stomach.

Lambert, Elmer John, Los Angeles; State University of Iowa College of Homeopathic Medicine, Iowa City, 1898; died Dec. 18, aged 83.

Landon, Lyndon Holt Ⓜ Pittsburgh; University of Pennsylvania School of Medicine, Philadelphia, 1910; veteran of World War I and was awarded the Victory Medal, the American Defense Medal, and the French Verdun Defense Medal; specialist certified by the American Board of Surgery; fellow of the International College of Surgeons and the American College of Surgeons; member of the American College of Gastroenterology; past-president of the Pittsburgh Surgical Society; associated with the Montefiore Hospital and the Western Pennsylvania Hospital, where he died Jan. 11, aged 73, of bronchopneumonia.

Lazell, Edward William, Santa Barbara, Calif.; Denver College of Medicine, 1902; veteran of the Spanish-American War and World War I; for many years associated with the Veterans Administration in Denver; died in the Veterans Administration Hospital, Los Angeles, Jan. 5, aged 81.

Lerman, Simon Edward Ⓜ Van Dyke, Mich.; Detroit College of Medicine and Surgery, 1939; interned at the Eloise (Mich.) Hospital; served a residency at the Children's Hospital in Detroit; member of the American Academy of General Practice; associated with the Memorial Hospital; died in Detroit Jan. 14, aged 47.

Logan, Vonando Green, American Falls, Idaho; University of Louisville (Ky.) Medical Department, 1905; veteran of the Spanish-American War and veteran of World War I; served as health officer of Power County; on the staff of the Schiltz Memorial Hospital, where he died Jan. 6, aged 83, of cerebral embolus and polycythemia vera.

Lovely, Frank Thomas Ⓜ Omaha; Creighton University School of Medicine, Omaha, 1919; member of the American Academy of General Practice; served as police surgeon; died Jan. 2, aged 65.

Lubell, Moses Freed, Waterville, Maine; Columbia University College of Physicians and Surgeons, New York City, 1925; specialist certified by the American Board of Radiology; member of the American Roentgen Ray Society, Radiological Society of North America, and the American College of Radiology; on the staff of the Sisters' Hospital; died Jan. 13, aged 59.

Lynn, John Galloway IV, Honolulu, Hawaii; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1929; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychosomatic Society, American Psychiatric Association, Association for Research in Nervous and Mental Diseases, and the American Psychopathological Association; associated with the Queen's General Hospital; died Dec. 22, aged 56.

McCoy, Bernard E., Spokane, Wash.; Barnes Medical College, St. Louis, 1905; died Jan. 10, aged 81, of coronary thrombosis.

McDill, Donald Samuel, Lima, Ohio; Ohio State University College of Medicine, Columbus, 1930; veteran of World War I; served as coroner of Coshocton and as health commissioner of the city of Coshocton; associated with the Lima State Hospital; died in St. Rita's Hospital Jan. 15, aged 65, of subarachnoid hemorrhage.

McMillan, William Thomas, Los Angeles; Jefferson Medical College of Philadelphia, 1897; died in the Madison Lodge Sanitarium Jan. 12, aged 88.

MacLain, Marshall Mackey, Leesburg, Fla.; Maryland Medical College, Baltimore, 1913; veteran of World War I; retired from the Veterans Administration in Washington, D. C., on Jan. 31, 1950; died in the Durham Young Hospital Jan. 9, aged 69, of cor pulmonale due to pulmonary fibrosis.

Maby, Aloysius DeWitt, Boston; New York Homeopathic Medical College and Flower Hospital, New York City, 1916; veteran of World War I; for many years associated with the Veterans Administration; died Jan. 15, aged 65.

Manzella, Louis Girard Ⓜ Buffalo; University of Buffalo School of Medicine, 1921; past-president of the Canisius College Alumni Association; for many years affiliated with the Sisters of Charity Hospital and the Emergency Hospital, where he died Jan. 14, aged 64, of coronary occlusion.

Margossian, Arshag Der Ⓜ Providence, R. I.; Jefferson Medical College of Philadelphia, 1901; affiliated with the Roger Williams Hospital, St. Joseph's Hospital, and Miriam Hospital; died in the Rhode Island Hospital Jan. 9, aged 84.

Markel, Ivan James Ⓜ Elkhart, Ind.; Rush Medical College, Chicago, 1911; veteran of World War I; affiliated with the Elkhart General Hospital, where he died Jan. 7, aged 73, of coronary disease.

Metcalf, John William Ⓜ Toronto, Ohio; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1920; veteran of World War I; affiliated with Ohio Valley General Hospital, Gill Memorial Hospital in Steubenville, and Weirton General Hospital in Weirton, W. Va.; for many years physician for the schools in Toronto; died Jan. 6, aged 65, of congestive heart failure.

Miller, Jared Homer, Pasadena, Calif.; Baltimore Medical College, 1900; died Jan. 16, aged 89.

Mott, James R. Ⓜ Hartville, Mo.; St. Louis College of Physicians and Surgeons, 1907; died Jan. 9, aged 82.

Mulkey, James Robert Ⓜ Fayetteville, Ark.; University of Louisville (Ky.) School of Medicine, 1934; veteran of World War II; affiliated with the Veterans Administration Hospital; died Jan. 14, aged 51.

Mulstein, Adolph, New York City; University of Maryland School of Medicine, Baltimore, 1911; died Jan. 12, aged 81.

Nalchajian, Dikran Davis Ⓜ Chelsea, Mass.; Boston University School of Medicine, 1899; for many years on the staffs of the Chelsea (Mass.) Memorial Hospital and the Whidden Memorial Hospital in Everett, where he died Jan. 8, aged 87.

Nelson, Harry Ⓜ Woodbury, N. J.; University of Pennsylvania School of Medicine, Philadelphia, 1923; member of the American Fracture Association; member of the staff of the Underwood Hospital; died in Washington, D. C., Jan. 7, aged 63.

Nice, Charles McKinney Ⓜ Birmingham, Ala.; University of Pennsylvania Department of Medicine, Philadelphia, 1904; fellow of the American College of Physicians; served on the staffs of St. Vincent's Hospital, South Highlands Infirmary, and the Hillman Hospital; died Jan. 11, aged 77.

Numbers, Don S., Boise, Idaho; National University of Arts and Sciences Medical Department, St. Louis, 1914; veteran of World War I; died in the Veterans Administration Center Jan. 18, aged 70, of carcinoma of the ampulla vater.

Orton, Susanne, Darlington, Wis.; Northwestern University Woman's Medical School, Chicago, 1900; died in the Memorial Hospital Jan. 9, aged 88.

Park, James A., Columbus, Ohio; Columbus Medical College, 1892; died Jan. 9, aged 91.

Persinger, Carey, Washington C. H., Ohio; Starling Medical College, Columbus, 1898; died Jan. 12, aged 91.

Pierce, Reuel Alfred, Worcester, Mass.; Boston University School of Medicine, 1912; veteran of World War I; died in the City Hospital Jan. 7, aged 70.

Plannette, Herbert Leslie Ⓜ Whittier, Calif.; University of Wooster Medical Department, Cleveland, 1905; died Jan. 12, aged 83.

Price, David Richard, Columbus, Ohio; Eclectic Medical College, Cincinnati, 1918; died in the Grant Hospital Jan. 13, aged 68, of heart disease.

Rand, Richard Foster Ⓜ Center Harbor, N. H.; Johns Hopkins University School of Medicine, Baltimore, 1900; served on the faculty of Yale University School of Medicine in New Haven, Conn.; past-president of the Connecticut State Medical Society and the New Haven (Conn.) County Medical Society; fellow of the American College of Surgeons; died Jan. 18, aged 91.

Solis-Cohen, Myer Ⓜ Philadelphia; University of Pennsylvania Department of Medicine, Philadelphia, 1900; served on the faculty of his alma mater and the University of Pennsylvania Graduate School of Medicine; formerly lecturer in medical jurisprudence and toxicology at the Woman's Medical College of Pennsylvania; at one time assistant director of public health for Philadelphia; served in France during World War I; associated with the Eagleville (Pa.) Sanatorium; author of many books; died in the Hospital of the University of Pennsylvania Jan. 8, aged 82.

Spizzirri, Alberto, St. Louis; Universita di Napoli Facolta di Medicina e Chirurgia, Italy, 1916; died at his home in Lemay, Mo., Jan. 7, aged 73.

Sprinkle, Willis McCollum, Marion, Va.; University of Cincinnati College of Medicine, 1927; died in Abingdon Jan. 1, aged 61.

Staub, J. Howard Ⓜ Stamford, Conn.; Long Island College Hospital, Brooklyn, 1899; past-president and vice-president of the Fairfield County Medical Society; fellow of the American College of Surgeons; served as chairman of the Stamford Fidelity Bank and Trust Company; for many years associated with the Stamford Hospital, where he died Jan. 10, aged 84.

Stewart, David Lloyd Ⓜ San Antonio, Texas; Chicago College of Medicine and Surgery, 1909; retired from the regular Army Oct. 31, 1942; died Sept. 26, aged 76.

Stiers, Frederick Loren Ⓜ East Peoria, Ill.; Washington University School of Medicine, St. Louis, 1903; served as a member of the East Peoria Grade School Board of Education and a member of the city council; for many years health officer for the city of East Peoria; served as health officer for Fondulac Township; associated with the Proctor Community Hospital, Peoria, where he was past-president of the hospital board; died Dec. 23, aged 84.

Strohschein, Donald Frederic Ⓜ Detroit; Detroit College of Medicine and Surgery, 1930; associated with the Northwestern Branch of the Grace Hospital; past-president of the alumni association of his alma mater; died in the Henry Ford Hospital Dec. 14, aged 55.

Szumer, Lipa, New York City; Medizinische Fakultät der Universität, Vienna, Austria, 1915; died Nov. 19, aged 72.

Tarleton, Francis Samuel Ⓜ Hot Springs National Park, Ark.; Tulane University School of Medicine, New Orleans, 1917; past-president of the Garland County Medical Society; veteran of World War I; a member of the staffs of Quachita General Hospital and St. Joseph's Infirmary, where he died Jan. 3, aged 66, of acute congestive heart disease.

Theiss, Frederick Charles Ⓜ Cincinnati; Medical College of Ohio, Cincinnati, 1901; served on the staffs of the Evangelical Deaconess Hospital and the Good Samaritan Hospital, where he died Jan. 2, aged 83, of arteriosclerotic heart disease with congestive failure.

Thomas, Allen Jones, Sulphur Springs, Texas (licensed in Texas, under the Act of 1907); died in Quanah Dec. 31, aged 80.

Tilley, William Taft, South Burlington, Vt.; University of Vermont College of Medicine, Burlington, 1900; veteran of World War I; died Dec. 29, aged 86.

Timberlake, Harold Paul Ⓜ Cleveland; Ohio State University College of Medicine, Columbus, 1917; veteran of World Wars I and II; chief medical officer of the Cleveland division of the Veterans Administration; died in the Polyclinic Hospital Dec. 24, aged 68.

Todd, Lester Claire Ⓜ Charlotte, N. C.; University of Michigan Medical School, Ann Arbor, 1918; specialist certified by the American Board of Pathology; member of the American College of Allergists; past-president of the Southeastern Allergy Association; and the North Carolina Pathological Society; veteran of World War I; associated with the Presbyterian Hospital and the Charlotte Memorial Hospital, where he died Dec. 29, aged 71, of rupture of abdominal aortic aneurysm.

Trickey, Charles Lemuel, Asheville, N. C.; Dartmouth Medical School, Hanover, N. H., 1910; specialist certified by the American Board of Psychiatry and Neurology; veteran of World War I; formerly assistant superintendent of Wrentham (Mass.) State School; died Dec. 12, aged 71.

Triplett, William Romulus, Purlear, N. C.; North Carolina Medical College, Charlotte, 1914; died in Davis Hospital, Statesville, Jan. 6, aged 79.

Van Gaasbeck, Chester Bruce, Kingston, N. Y.; Albany (N. Y.) Medical College, 1917; veteran of World War I; served in the regular Navy; for many years secretary of the Ulster County Medical Society; member of the staff of the Kingston Hospital; honorary police surgeon; died Jan. 4, aged 65, of coronary disease.

Van Norman, Karl Halifax, Mercer Island, Wash.; born in 1882; University of Toronto Faculty of Medicine, Toronto, Ont., Canada, 1904; past-president of the Washington State Hospital Association and a vice-president of the Seattle Hospital Council; a charter member of the American College of Hospital Administrators and a life member of the American Hospital Association; at one time superintendent of Charles T. Miller Hospital in St. Paul, general superintendent of the King County Hospital System in Seattle, a director at the Western Reserve University Hospital group in Cleveland, and director and secretary of the board of trustees of the Doctors Hospital in Seattle; died Dec. 24, aged 77.

Vinup, Frederick Henry Ⓜ Baltimore; University of Maryland School of Medicine, Baltimore, 1909; member of the Radiological Society of North America, Industrial Medical Association, and the Association of Life Insurance Medical Directors of America; served with the city health department, the welfare board, and as president of the board of police examiners; for many years medical director of the Monumental Life Insurance Company; veteran of World War I; died Jan. 3, aged 74.

Wagers, Arthur James Ⓜ Philadelphia; Washington University School of Medicine, St. Louis, 1911; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; clinical professor of laryngology at Jefferson Medical College; veteran of World War I; associated with the Jefferson Medical College Hospital; died Dec. 18, aged 83.

Walker, Frank Columbia Ⓜ Indianapolis; Rush Medical College, Chicago, 1907; specialist certified by the American Board of Obstetrics and Gynecology; member of the Central Association of Obstetricians and Gynecologists; fellow of the American College of Surgeons; for many years on the faculty of the Indiana University School of Medicine; veteran of World War I; served on the staff of the Methodist Hospital, where he died Jan. 3, aged 79, of coronary embolus.

Waller, Clifford Ellison Ⓢ Medical Director, U. S. Public Health Service, retired, Silver Spring, Md.; born April 1, 1886; George Washington University School of Medicine, Washington, D. C., 1910; from 1910 to 1913 a medical officer in the Indian Service; commissioned in the U. S. Public Health Service in 1914, retiring April 1, 1940; served as assistant surgeon general in charge of the states relations division of the U. S. Public Health Service; formerly associated with the State Bureau of Public Health of New Mexico; past-president of the Southern Branch of the American Public Health Association; member of the Association of Military Surgeons of the United States; at one time health officer of Loudoun County, Va.; died in the Walter Reed Army Hospital, Washington, D. C., Jan. 4, aged 73.

Walters, James Walker Ⓢ Lynchburg, Va.; Medical College of Virginia, Richmond, 1905; veteran of World War I; died Dec. 27, aged 79.

Weiss, Edward Ⓢ Philadelphia; born July 30, 1895; Jefferson Medical College of Philadelphia, 1917; specialist certified by the American Board of Internal Medicine; member of the American Rheumatism Association; a founder and past-president of the American Psychosomatic Society; past-president of the American Society for Research in Psychosomatic Problems; fellow of the American College of Physicians; a director of a fund for research in psychosomatic medicine of the National Committee for Mental Hygiene; served as professor of clinical medicine at Temple University School of Medicine; formerly instructor of pathology at his alma mater; on the staff of the Temple University Hospital; author of many books; joint author of "Psychosomatic Medicine"; died Jan. 13, aged 64.

White, William Francis Ⓢ Wellsboro, Pa.; Jefferson Medical College of Philadelphia, 1914; for many years coroner of Tioga County; member of the Industrial Medical Association; veteran of World War II; past-president and a director of Tioga County Cancer Society; served as county medical director; on the staff of the Blossburg (Pa.) State Hospital; consulting physician for Borden Food Products Company in Wellsboro; died in the George F. Geisinger Memorial Hospital, Danville, Dec. 12, aged 69.

Whitsell, John C. Ⓢ St. Joseph, Mo.; Ensworth Medical College, St. Joseph, 1903; served as mayor of St. Joseph; associated with Missouri Methodist and St. Joseph's hospitals; died Dec. 27, aged 84, of bronchopneumonia.

Williams, Edmund Percy Ⓢ Oakland, Maine; Medical School of Maine, Portland, 1908; died Dec. 30, aged 83.

Williams, Minor L. Ⓢ Robstown, Texas (licensed in Texas under the Act of 1907); past-president of the Nueces County Medical Society; died in Corpus Christi Dec. 29, aged 89.

Witherspoon, Ezra Offutt Ⓢ Louisville, Ky.; Hospital College of Medicine, Louisville, 1901; for many years assistant health officer for the city of Louisville; associated with SS Mary and Elizabeth Hospital, St. Anthony's Hospital, and the Kentucky Baptist Hospital; died Jan. 3, aged 81, of myocardial failure.

Wolff, Nathaniel Stein, New York City; University and Bellevue Hospital Medical College, New York City, 1925; member of the American Psychiatric Association; died in London, England, Dec. 22, aged 64.

Wood, Joshua Powell Sr., Altadena, Calif.; Medical Department of Tulane University of Louisiana, New Orleans, 1910; for many years associated with the Veterans Administration Hospital, Tucson, Ariz.; died in Palo Alto Dec. 23, aged 80.

Worthington, Lois Claire Ⓢ Bakersfield, Calif.; Cooper Medical College, San Francisco, 1897; died Dec. 20, aged 84.

Wright, George William Ⓢ Monroe, La.; Medical Department of Tulane University of Louisiana, New Orleans, 1916; past-president of the Quachita Parish Medical Society, Louisiana State Medical Society, and Louisiana Surgical Society; fellow of the International College of Surgeons and the American College of Surgeons; veteran of World War I; on the staff of E. A. Conway Hospital, Memorial Hospital, and the Wright–Bendel Clinic, where he died Jan. 7, aged 67.

Yarnell, Oscar, Long Beach, Calif.; St. Louis College of Physicians and Surgeons, 1897; veteran of World War I; formerly associated with the U. S. Public Health Service; died in the Long Beach Hospital Dec. 25, aged 85, of cerebral thrombosis.

Yocom, Frank Willis Ⓢ Lynwood, Calif.; University of California School of Medicine, San Francisco, 1922; member of the Radiological Society of North America; fellow of the International College of Surgeons; died Dec. 29, aged 75.

Zipser, Jacques Ephraim Ⓢ New York City; Bellevue Hospital Medical College, New York City, 1896; died Oct. 24, aged 86, of myocardial infarct and arteriosclerotic heart disease.

Zuerndorfer, Louis, New York City; Julius–Maximilians Universität Medizinische Fakultät, Wurzburg, Bavaria, Germany, 1907; died Jan. 7, aged 78, of coronary occlusion, hypertensive heart disease, and chronic nephritis.

FOREIGN LETTERS

AUSTRIA

The Galea Aponeurotica.—At the meeting of the Society of Physicians in Vienna on Dec. 18, Dr. H. Hayek stated that all textbooks describe the galea aponeurotica as a tendon band which lies between the frontal and the occipital muscles and is connected with the scalp by the overlying skin. This description is not only incomplete but also partly incorrect. The galea is not only an intermediary tendon between the two muscles; it also extends underneath the frontal muscle between that muscle and the periosteum of the frontal bone as a strong band and reaches the margin of the orbit, where it adheres closely to the bone. Thus one has to differentiate between a parietal part of the galea, which lies just beneath the skin, and the frontal part, which lies under the frontal muscle. The strong adherence to the bone is fully developed not only in the adult but also in the infant. The adherence of the galea to the bone can also be demonstrated on the living subject by pulling the scalp backwards by the hair. If one does this to himself he will feel the tension of the pars frontalis of the galea at its epiphysis.

Baldness and Tension Headaches.—At the same meeting Dr. H. Humplik stated that premature baldness is believed to be caused by pressure atrophy of the hair papilla, which develops during or after puberty. The information about the position of the galea aponeurotica which is given in textbooks of anatomy has been refuted, and the new anatomic knowledge makes the problem of premature baldness appear in a new light. Galeatomy relaxes the galea and decreases the pressure on the hair papilla. By means of this operation it was possible completely to eliminate the so-called tension headache, which is located in the area of the forehead and radiates towards the temple and the vertex, in 92% of 124 patients on whom the operation was performed.

DENMARK

The Metabolic Effect of New Anabolic Steroids.—K. Brøchner-Mortensen and co-workers (*Acta med. scandinav.* 165:197-205, 1959) studied the nitrogen, calcium, and phosphorus balance in five patients with chronic rheumatoid arthritis to determine whether the new 19-nor-steroids, norethandrolone and nandrolone phenpropionate, were capable of inhibiting the excess excretion of nitrogen and calcium, which developed as an undesirable side-effect in prednisone treatment. The investigation showed convincingly that the catabolic action of prednisone could be inhibited if an anabolic 19-nor-steroid was administered concurrently. The action of the 19-nor-steroids on the calcium balance was less obvious, particularly in the case of bedridden patients. In one patient, however, there was a convincing effect from 19-nor-steroid, both when it was administered alone and in combination with prednisone. In two of the four women there was a vaguely increased hirsutism of the upper lip, but apart from this there was no virilization and no need to discontinue treatment.

Norethandrolone, however, in contrast to nandrolone, showed a strong progestational effect, which reduced its practical clinical value as an anabolic compound. The action of injected nandrolone was much stronger and persisted much longer than the action of norethandrolone given perorally. In the limited material of the present study neither drug appeared to inhibit the beneficial action of prednisone on the articular symptoms. The investigation appeared to demonstrate that the administration of 19-nor-steroids could counteract certain undesirable metabolic effects in the long-term treatment with prednisone. The practical significance of this combination therapy cannot be evaluated until it has been used in a larger series. The authors recommended that, when such investigations are undertaken, due attention be paid to the fact that almost nothing is known about possible hazards in long-term 19-nor-steroid therapy.

Mild Chronic Pancreatitis.—Of nine patients with chronic pancreatitis studied by Poul Efferse (*Acta med. scandinav.* 165:115-124, 1959), four had the typical chronic relapsing type. The remaining five did not have classic attacks of acute pancreatitis accompanied by severe pain but only mild to moderate epigastric pain which did not require the use of morphine or emergency admission to hospital. At times these five patients with mild chronic pancreatitis had slight to moderate steatorrhea, and one of them had a transitory exacerbation of diabetes. None of these five patients developed calcifications of the pancreas, enlargement of the pancreas, or jaundice, despite a duration of the disease ranging from 7 to 25 years. Two showed signs of diabetes. Addiction to alcohol did not occur among them.

In order to recognize the mild form, otherwise so likely to be misinterpreted as abdominal psychoneurosis, it is important to ascertain whether the patients have had grey stools without simultaneous

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The items in these letters are contributed by regular correspondents in the various foreign countries.

jaundice and to examine them for steatorrhea and creatorrhea, to perform glucose tolerance tests, and to determine the urinary diastase in patients with uncharacteristic epigastric pain. The author concluded that this mild form of chronic pancreatitis was presumably more common than the surgical type, but as a rule it remained undiagnosed.

FINLAND

Traumatic Diaphragmatic Hernia.—Laustela and Tala (*Ann. chir. et gynaec. Fenniae,* supp. 87, vol. 48, 1959) reported a series of 23 patients with traumatic diaphragmatic hernia. The hernia of 12 was secondary to a war injury. The trauma responsible for the diphragmatic defect in the 11 civilians was a stab wound of the chest in 4, an automobile accident in 3, hyperemesis in 2, a blow on the abdomen in 1, and falling from a height of 10 meters in 1. In the two with hernia on the right side, the liver, but no other abdominal viscera, had herniated into the thoracic cavity. In those with hernia on the left side the most commonly dislocated organs were the omentum, colon, stomach, and small intestine. The spleen had penetrated above the diaphragm in four and part of the pancreas in two. The commonest symptoms referable to the hernia were abdominal pain, vomiting, swelling in the abdomen, and meteorism. Dyspnea occurred as the sole symptom in five patients and chest pain in two. Four patients were nearly asymptomatic. On account of symptoms of obstruction and strangulation of the herniated abdominal viscera, laparotomy had to be performed as an emergency operation on three patients. No intestinal or gastric resection was necessary in these patients.

For all 23 patients correction of the diaphragmatic hernia was performed by thoracotomy. Postoperative complications were more frequent with military patients than with the civilians because the former were treated under field conditions without protection or antibiotics. The authors concluded that the late results of the operative treatment of diaphragmatic hernia could be considered good in six and satisfactory in three of the military patients. Seven of them practiced their previous occupation or one similar to it, and two had taken up less strenuous work. Of the civilians nine had resumed their previous work, and they were found to be in generally good condition. Two patients had slight symptoms in the chest or abdomen.

Thyroid Crisis.—B. A. Lamberg (*Acta med. scandinav.* 164:479-496, 1959) stated that since goiter was endemic in Finland, masked forms of thyrotoxicosis might occur and might end in a thyroid crisis if not promptly diagnosed. He observed a series of 17 patients with crisis (10) or impending crisis (7). Some of these also suffered from some complicating disease or diseases. The precipitating causes were classified as (1) spontaneous (idiopathic), (2) some stress factor, (3) the discontinuation of iodine or thyrostatic therapy, or (4) the institution of radioiodine therapy. Four of the patients with impending crisis and five of those with manifest crisis died. The death rate was thus more than 50%, but all of these patients did not die in the critical phase. Some of them pulled through this stage and died of the irreparable damages caused by the crisis. The crisis could not be explained as iodopenia. The life-saving role of the large doses of iodine could be explained only by postulating some peripheral effect of iodine which occurred only when large doses were given. Lamberg concluded that the explanation of the beneficial effect of the thyroxine therapy might be that the thyroxine administered in some way influenced the metabolism and caused a stabilization of the relations between the various thyroid hormones or between hormones and their analogs in the peripheral tissues.

FRANCE

Parahydroxyphenylethylamine and Hepatomegaly.—R. Lutembacher (*Arch. mal. coeur,* Feb., 1959) used p-hydroxyphenylethylamine to treat patients with hepatomegaly which persisted after treatment with active cardiac tonics. In patients with rheumatic fever hepatomegaly results from a histaminic imbalance. The author injected 10 mg. of the drug dissolved in 3 cc. of Ringer's solution into patients and gave a second injection 15 minutes later. To obtain a definite reduction in the size of the liver, digitalis should also be given. The p-hydroxyphenylethylamine exerts an antagonistic action on histamine and reduces the size of the liver only when the enlargement is caused by a histaminic imbalance.

Cardiac Arrest.—Gentilli and de Nunno (*Lyon chir.* 55:559 [July] 1959) reported the case of two patients in whom cardiac arrest occurred while they were undergoing cardiotomy. The heart in both patients was distended and cyanotic. Cardiac massage and injections of epinephrine into the cardiac cavity failed to restore contraction. Because of the distention of the right auricle the authors aspirated 40 and 60 cc. of blood, respectively, from the auricles of the two patients. As soon as this was done and massage was reapplied, normal cardiac rhythm was resumed in both patients. The authors believed that the withdrawal of blood from the auricle precipitated a sudden fall in the auricular tension and permitted the discharge of blood from the coronary veins, thus permitting reestablishment of normal coronary circulation.

Vitamin C and Phenylbutazone.—Phenylbutazone exerts an anti-inflammatory effect similar to that of cortisone, but unlike cortisone it acts directly on the tissues. Its chief drawback is the production of such untoward side-effects as gastralgia and peptic ulcer. Encouraged by experimental studies on guinea pigs, M. Lyon gave a series of 230 patients phenylbutazone combined with vitamin C, and no untoward reaction occurred in any of these patients.

INDIA

Lathyrism.—K. K. Govil and co-workers (*J. Indian M. A.*, vol. 33, Dec. 16, 1959) stated that lathyrism is seen frequently in certain parts of India where the total disability from this disease imposes a serious drain on the agricultural manpower. The persons affected were usually manual laborers and farmers who lived in poor economic conditions with primitive environmental sanitation. A series of 563 patients included all age groups except 0 to 3, the highest incidence being seen between the ages 11 and 30 years. This high incidence may have been due to the greater amount of food consumed and greater exposure to stress and fatigue at this period of life. Of the total number of patients 93.1% were men. Of the total number 75% were single which indicated that factors other than diet were responsible for the disease. Most of the cases occurred in August, September, and October.

The onset was sudden in 39.4% of the patients, who felt heavy in the legs and were unable to walk without mental or sensory disturbances, mostly while working in rains or floods. In 60.6% the onset was gradual and consisted of pain in the lumbar region and cramps in muscles of the calf. The course of the disease was slow. The general physical appearance of the patients was good. Reflexes were normal in the upper and exaggerated in the lower extremities. Samples of diets eaten by these people contained 25 to 90% Lathyrus sativus grains. Therapeutic trials were given with vitamin B_{12}, vitamin B complex, multivitamin tablets, and muscle relaxants, but with no appreciable improvement.

Diagnosis of Tuberculous Lymph Node Perforation into Bronchus.—Mathur and Bahadur (*J. Indian M. A.*, vol. 34, January, 1960) stated that perforation of a caseous lymph node into the bronchial tree is common in children and influences the course of the tuberculous infection. Such perforation has also been reported by some authors in adolescents and adults who were examined with a bronchoscope. If it did occur it would have serious implications, as an active perforation persisting after resection of a lung segment might lead to reactivation of the disease.

The authors therefore studied 300 patients who had been proved to have pulmonary tuberculosis and who had undergone bronchoscopy under local anesthesia in addition to the routine clinical examination. Bronchotelescopes were used for detailed examination of the bronchial tree to detect lymph node perforation. Broad irregular funnel-shaped openings in the bronchial wall surrounded by and partially filled with coarse granulations or furuncle-like elevation of the mucosa, with a central umbilication and exudation of purulent material on pressure, from which scars are formed, were taken as pathognomonic signs of lymph node perforation. Round circumscribed openings, funnel-shaped or star-like mucosal scars, humps, or callous prominences with local discoloration of the mucosa or isolated patches of anthracotic pigmentations were taken as suggestive signs. The disease was mainly exudative in 75%, productive in 13%, and fibrotic in 12%. None of the patients showed the pathognomonic signs of lymph node perforation on bronchoscopic examination, but 41 showed suggestive signs. The appearance of holes was found to be constant on repeated bronchoscopic examinations.

Biopsy performed in six of these patients showed dilated submucous glands and infiltration with lymphocytes or typical tuberculous granulation tissue in the wall. The mucosal scars in five patients were situated at the orifice of the bronchus leading to the main parenchymal lesion. All of these had far advanced parenchymatous disease. The x-ray findings were suggestive of an obstructive lesion in four patients without any evidence of an endobronchial lesion to explain the obstructive appearance. Thus none of the patients showed evidence of recent lymph node perforation. The authors did not consider mucosal holes conclusive evidence of lymph node perforation. They were probably openings of diseased excretory ducts from mucous glands as was suggested by the biopsy specimens. The mucosal scars, however, could be considered as remnants of former lymph node perforations.

Progress of Health Programs.—In a broadcast from New Delhi in December the Union Health Minister said that infant mortality had decreased from 160 to less than 100 per 1,000 population. The general death rate, which ranged between 20 and 25 persons per 1,000 in the last decade, had come down to 10 and 12 persons per 1,000. The expectation of life had risen from 32 to 42 years. The health schemes drawn up after independence have stressed disease prevention. A national tuberculosis institute had been established in Bangalore for training doctors, nurses, health visitors, social workers, and technicians.

The national water supply and sanitation program was an important feature of the five-year health plans. Nearly 33% of the total outlay on health in the second plan was earmarked for this program. As a result 193 water supply and 57 drainage schemes were initiated. Most of these were expected to be completed during the second plan. The minister hoped that eventually there would be one doctor for every 5,000 persons, or about 90,000 doctors in the entire country. At the end of the first plan there were 69,000, but by the end of the second plan the number should be over 80,000. The training programs for nurses have been stepped up to turn out 2,000 nurses every year, and it was hoped that there would be 30,000 trained nurses by 1961.

NORWAY

The Drug-Confused Motorist.—Tablets containing 0.4 Gm. of meprobamate have of late come largely to replace chlorpromazine in the treatment of various psychoses and other mental ailments. Dr. C. L. Laane (*Tidsskr. norske laegefor.*, Jan. 1, 1960) called special attention to the risks run by motor drivers who take this drug. The lassitude and giddiness it may induce may be interpreted as alcohol poisoning with the result that the driver is arrested and subjected to a blood test for alcohol. Both the authorities and the man in the street should be informed of this risk, and the physician who prescribes the drug should bring this risk to his patient's notice.

SWEDEN

Barbiturate Poisoning.—Hed and von Reis (*Acta med. scandinav.* 165:431-435, 1959) determined the glutamic-oxalacetic transaminase (GOT), glutamic-puruvic transaminase (GPT), lactic dehydrogenase (LD), and aldolase activity in 25 patients with barbiturate poisoning. In 12 the enzyme activity showed normal values, and in 13 it was pathologically elevated. In 10 of these patients the enzyme pattern was of the muscle type and in 1 of the liver type. In two patients two peaks of enzyme activity occurred, the first patient showing a muscle pattern and the second a liver pattern. The second peak of enzyme activity of the liver type in these two patients was not accompanied by renewed elevation of LD and aldolase. The enzyme activity peaks presenting muscle patterns occurred within two days after the patient's admission to the hospital, while the liver patterns did not appear until after four or five days. In barbiturate poisoning, pain, tenderness, and edema in the musculature were not unusual symptoms. Even grave muscle damage with necrosis and myoglobinuria could occur when no abnormal pressure had been applied to the musculature. In barbiturate poisoning there was no relationship between the elevation of enzyme activity and the duration of the comatose state. In view of these data it seemed less probable that the pressure on the musculature during the comatose stage could be the only cause of the transaminase increase in these patients with barbiturate poisoning.

Böttinger and Östman (*Acta med. scandinav.* 165:437-444, 1959) stated that a study of 311 patients with barbiturate intoxication showed a continued marked increase in the number of such patients admitted to the hospital. All patients were treated without central analeptics. No deaths occurred. In a two-year period 20 patients, representing 58% of those with severe cases (those who were unconscious for more than 24 hours after admission), were treated with bemegride. Commenting on the material, the authors stated that women predominated, especially in the younger age groups and among those with mild cases, but that women did not predominate in the total number of suicides in Sweden, of which 70 to 80% were committed by men. The predominance of women among cases of barbiturate intoxication was evidence only that women preferred this particular method.

Most patients were between 21 and 50 years of age. Of the men 73% and of the women 85% were in this age group. Only 18% of the cases were severe and associated with prolonged coma. There was a marked reduction (12% in this series) in the use of phenobarbital, but the use of amobarbital increased to 39%. In 1944 only 17% of those with barbiturate poisoning had used amobarbital. This shift from the slowly eliminated phenobarbital to the shorter acting drug improved the prognosis. The combination of barbiturate and alcohol intoxication was present in at least 14% of this series. The authors considered bemegride to be a central analeptic of some value as a respiratory stimulant but not a specific antibarbituric agent. An early tracheotomy was used when the patient did not regain consciousness promptly. In the presence of advanced hypotension levarterenol should be used.

Tick-Borne Meningoencephalomyelitis.—In recent years the presence of meningoencephalomyelitis caused by agents related to the Russian tick-borne encephalitis viruses has been reported not only from Russia but also from Czechoslovakia, Hungary, Slovenia, Austria, Poland, Sweden, Finland, and Northern Ireland. Börje Holmgren and co-workers (*Acta med. scandinav.* 164:507-522, 1959) reported that of 176 patients hospitalized in Stockholm in the summer and fall of 1956 for acute infections involving the central nervous system 68 had complement-fixing and neutralizing antibodies against viruses of this group. During convalescence 30 of these patients showed a definite rise in antibody titer. Many of the patients with peak titer already in the first serum specimen were also experiencing an acute infection with the same virus. The clinical findings in the 68 patients with Russian tick-borne encephalitis antibodies were similar to those observed in patients in European Russia and Central Europe. Thus the disease had a biphasic course in about 70% of the patients.

Clinical signs of encephalitis, such as tremor, vertigo, ataxic gait, mental imbalance, and disturbance of sleep occurred in about half the patients. An electroencephalogram showing pathological findings was found in 70%. Transient paralyses were observed in about 25%. Convalescence lasted 2 to 14 months. For the serologic diagnosis of a tick-borne infection the spinal fluid reaction was simple and reliable, but the rapidity of antibody appearance and rise in the spinal fluid was variable. Although the titer in the spinal fluid sometimes continued to rise over an extended period, it was important to collect the first serum specimen as early as possible in order to increase the possibility of conclusive results. The second specimen should be collected three or four weeks after the onset of the major disease, as the titer should have reached its peak by this time.

Diagnosis Of Anemias.—Despite the great prevalence of iron deficiency anemia the early detection of iron deficiency and the differentiation between iron deficiency anemia and other anemias remain a clinical problem, according to Hansen and Weinfeld (*Acta med. scandinav.* 165:333-356, 1959). Hemosiderin and sideroblast assays were made in sternal marrow smears and squash preparation from 39 normal controls and 130 patients with blood dyscrasias. The values thus obtained were related to the hemoglobin, mean corpuscular hemoglobin, hypochromia, and serum iron levels. Hemosiderin and sideroblasts were generally well represented in the controls, which indicated adequate iron stores. In iron deficiency anemia hemosiderin, sideroblast, and serum iron levels were low.

In infectious toxic anemia with a low serum iron level without bleeding all patients had the normal number of sideroblasts and a normal or above-normal amount of hemosiderin. In other anemias (pernicious and hemolytic) both sideroblast and hemosiderin levels were above normal in most patients. Although the amount of hemosiderin could be taken as a rough measure of the size of the iron stores, the presence of sideroblasts merely indicated whether any iron was available. When the iron stores were on the point of running out, hemosiderin might be absent and the sideroblast percentage normal, indicating that some iron still was available for hemoglobin synthesis. The results of hemosiderin estimations and sideroblast counting regularly diverged in patients who had iron deficiency anemia with acute bleeding and during short-term treatment with iron by mouth. These divergences usually disappeared within a week after the patient had stopped bleeding, or the iron therapy was withdrawn. The authors recommended the combined use of hemosiderin estimation and sideroblast counting as it provided a more exact picture of the iron stores and available iron. A representative bone marrow specimen was required if the presence of hemosiderin was to be excluded.

Cerebral Circulation.—Professor Gustav Nylin and co-workers in Stockholm proved by using radioactive corpuscles that in healthy persons the blood in the cerebral vessels was totally renewed five or six times per minute. About 15% of all blood in the body flows through the brain. The total blood volume of the brain has, however, not yet been precisely determined. One liter of blood was found to pass through the brain of normal subjects in one hour. In a group of 12 patients suffering from cerebral vascular injuries with paralysis in whom roentgenograms did not reveal any constricted or occluded vessels, it was possible to detect a slow cerebral hemorrhage with the use of radioactive tracers.

Diabetes.—In recent years several oral preparations have been used in the treatment of diabetes. Sven Nilsson (*Acta med. scandinav.* 165:223-278, 1959) used Pascon tablets, each containing 300 mg. of para-aminobenzoic acid (PABA), 300 mg. of sodium salicylate, and 50 mg. of ascorbic acid, to treat 31 patients with diabetes. Most of the patients were elderly (only three were below 60 years of age). The first 20 patients started with a dose of 15 tablets a day. The rest received 3 Gm. of tolbutamide, 15 Pascon tablets, and 4.5 Gm. of PABA. A few were also given 4.5 Gm. of salicylic acid and 0.75 Gm. of ascorbic acid on consecutive days. In 16 of the 31 patients, Pascon produced a marked change in the carbohydrate metabolism. In 12 the blood sugar levels were satisfactory for one to four months afterwards. Four became worse after returning home. In another four the urine sugar level dropped more than 50% but to not less than 20 Gm. a day. In the remaining 11 Pascon produced no definite effect.

The side-effects of Pascon were few. A certain hypoglycemic effect appeared to be referable to the preparation. This sometimes lasted for a minimum of one month. It was believed that all of the components of the preparation had a depressive effect on the blood sugar level. It is possible that the addition of PABA and ascorbic acid enhanced not only the antirheumatic effect of the salicylate but also its hypoglycemic effect. Though less likely, it was possible that the hyperglycemia produced by a PABA or an ascorbic acid insufficiency might be controlled by simultaneous administration of these substances. PABA did not appear to exert its effect by inhibiting thyroid function.

UNITED KINGDOM

Electronic Clinical Thermometer.—An electronic clinical thermometer is undergoing clinical trial in the Royal Infirmary, Edinburgh. The instrument is connected to the patient by a wire, at the end of which is a sensitive probe that can be used for recording either rectal or oral temperatures. Heat produces electrical changes in this probe, and these changes are converted electronically into temperature readings which are read off on a dial. Any number of patients can be connected to the instrument, and, by moving a switch, the nurse can read the temperature of any patient connected to it. Not only is this thermometer more accurate than the ordinary clinical thermometer but it also records temperature in a matter of seconds. The main interest of the Edinburgh workers is in its use in recording temperatures in febrile patients, in whom frequent readings are necessary, without disturbing them. Another use is in controlling the temperature during the induction and maintenance of hypothermia. A further possible use is in reducing the amount of work involved in recording routine temperatures in a busy ward. It would allow, for instance, a nurse to record the temperatures of all the patients in a ward without moving from her office.

Perspex Icterometer.—Two reports by I. H. Gosset (*Lancet* 1:87, 1960) and P. E. Culley and others (*Lancet* 1:88, 1960) comment favorably on the value of a perspex icterometer in the diagnosis of jaundice in neonates. It consists of a curved strip of transparent perspex. On its convex surface are painted five transverse yellow strips in slightly different shades. These strips and the spaces between them are 3/16 in. wide. The strips are numbered 1 to 5, the lightest in color being 1. It is simply used by pressing the painted side against the tip of the baby's nose until the skin is blanched. The yellow color of the skin is then matched with the yellow strips on the scale. This simple instrument, which can be carried in the pocket and washed after use provides both a direct color match and a means of expressing the blood, with the resultant pink color, from the superficial skin layers. Experience suggests that, in patients other than those with rapidly increasing jaundice in the first 24 hours, if the icterometer reading is 3 or below serum levels need not be determined, whereas above this level blood studies should be undertaken.

New Journal.—A new specialty journal is being added to the list of those published by the British Medical Association. This is to be published in conjunction with the British Society of Gastroenterology and is to be called *Gut*. It will be published quarterly, and the first issue will appear late in March. The editor will be Mr. Harold Edwards, Surgeon to King's College Hospital.

Drug-Resistant Tuberculosis.—One of the greatest disasters that can befall a tuberculous patient is for the organisms to become resistant to two or more of the standard antituberculosis drugs. Poole and Stradling (*Brit. M. J.* 1:161, 1960) attributed this to treatment administered by general physicians who are unaware of the pitfalls. They analyzed records of 32 patients harboring initially sensitive tubercle bacilli, with resistance reported to one or more drugs after treatment. The courses of treatment recorded had been prescribed at a variety of hospitals, chest clinics, and sanitariums.

The information revealed that one main cause usually produced the first resistance to one drug (initial resistance). In 70% of the patients this was because the patient failed to take adequate amounts of the prescribed para-aminosalicylic acid (PAS). In 13% resistance developed in spite of the prescribing of PAS and isoniazid. Use of the drug to which the first resistance had developed was often continued although it gave no protective cover. Consequently resistance to other drugs followed (subsequent resistance). A total of 59 examples of drug resistance developed in the 32 patients; 29 occurred while the patient was under treatment at home, 22 in a sanitarium, and 8 in ordinary hospitals. In 18, faulty prescription of drugs was responsible for the resistance. This included the use of one drug alone, the use of one drug daily and the other intermittently, and the use of drugs of unproved value and mixtures of drugs.

The chief cause of resistance was an inadequate intake of PAS rather than of isoniazid. This can easily be understood as the dose of isoniazid is small and easily swallowed while the dose of PAS is large and cachets of it are unpleasant and distasteful. Urine tests showed that 11 of the patients failed to take PAS regularly. At least two of the three drugs that have proved to be of value should always be used together in long-term treatment and in adequate daily doses, namely, 1 Gm. of streptomycin, 200 mg. of isoniazid, and at least 10 Gm. of PAS, though preferably nearer 20 Gm. PAS should not be prescribed unless its administration can be fully supervised. Hinconstarch, thiosemicarbazone, and proprietary mixtures of drugs should never be prescribed. The tragic consequences of drug resistance in tuberculous patients is illustrated by the fact that 15 of the 32 in whom it occurred have died of the disease.

Delinquent Boys in Drug Test.—In a series of 15 boys in a reformatory, 8 were given pills containing hydroxyzine, a tranquilizer, by Dr. C. B. R. Pollock (*Medical Press*). The rest received a placebo. Housemasters, not knowing which boys had been given the drug, unerringly picked out those who had taken the tranquilizer as having improved most in disposition. The great difference between the two groups was that, although the boys who received the drug had the most outbursts of temper, they seemed to submit to their punishments with better grace.

Advanced Carcinoma of the Breast.—Because of the short-lived remissions after bilateral adrenalectomy and oophorectomy for the treatment of advanced breast cancer and the difficulty of maintaining them in electrolyte balance, Brinkling and Pillers (*Lancet* 1:123, 1960) decided to try the effect of bilateral oophorectomy and corticosteroid medication. A series of 82 patients with advanced carcinoma of the breast, graded stage 4, were selected for treatment. Most had been treated previously by radical surgery and radiotherapy. Several had received hormones, and it was not until remissions from this treatment were exhausted that bilateral oophorectomy was undertaken. A smaller group of patients seen for the first time with advanced disease was initially treated by oophorectomy and 10 mg. of prednisone given twice daily as soon as possible after operation.

The response to treatment was evaluated by careful clinical follow-up. A response was considered satisfactory if there was evidence of objective and subjective improvement enabling the patient to lead a relatively normal life again. A response was considered unsatisfactory if improvement was purely subjective. Sixteen patients were treated by oophorectomy as the first form of treatment, and nine of these had a satisfactory response. Their average survival time was 16 months compared with three months for the seven patients with an unsatisfactory response. The other 66 patients were treated when remissions produced by irradiation and hormone therapy were exhausted. Of these, 24 had a satisfactory response with an average survival time of 16½ months, compared with 6 months for the remaining 42 patients. Of 16 patients showing a satisfactory response, 10 were found to have hormone-dependent tumors, and of the 26 showing an unsatisfactory response there were 10 who had hormone-dependent tumors. The menopausal status, the presence of ovarian metastases, and the length of history before oophorectomy or liver involvement appeared to be of little prognostic significance. The authors concluded that bilateral oophorectomy and the administration of prednisone were useful palliative measures for patients with far advanced breast carcinoma.

Steroids in Severe Chronic Asthma.—According to David Phear and co-workers (*Lancet* 1:139, 1960) prolonged treatment with steroids is justified and valuable in a small carefully selected group of patients who are severely disabled by chronic or frequently recurring asthma. This conclusion was based on their findings in a group of 50 patients aged 23 to 66 years who had severe chronic asthma, were resistant to conventional treatments, but who were responding to steroids for the first time. Most of them had been unable to work or perform household duties for many months, and frequent hospital admission had been necessary. The mean duration of asthma was 10.3 years. Cortisone was given orally to 30 patients, most of whom needed 50 to 75 mg. daily. ACTH proved more effective in 4, and 16 were treated with prednisone. Good results were obtained in 39 patients, and there was moderate improvement in another 5. The results were poor in two women and one man with infective asthma, and three patients died during treatment. None of the deaths were associated with steroid therapy. Side-effects were slight except in the patients with depression. Twenty-one patients, previously unable to work, resumed their regular jobs or household duties.

Chronic Bronchitis.—A double-blind controlled trial of oxytetracycline in mild or moderately severe exacerbations of chronic bronchitis was described by a group of nine general practitioners working in cooperation with the London Public Health Laboratory (*Lancet* 1:137, 1960). This disease is now one frequently seen in general practice in Britain, particularly in industrial areas. Patients were randomly selected whenever possible, although no patient whose condition was serious was refused antibiotic treatment. Patients were graded into five groups according to the severity of the condition, and this grading was based on a functional assessment of the patient's physical capacity.

The severity of the exacerbation of the disease was assessed on a four-point scale when first seen and after 2, 7, and 14 days. A record was also made of sex, age, presence or absence of cough, sputum, purulent sputum, dyspnea, and fever. Sputum cultures were made at the beginning and end of treatment. The results showed that patients with a more than mild exacerbation of bronchitis derived measurable benefit from taking 250 mg. of oxytetracycline four times daily for five days. They recovered sooner and deteriorated less often than controls given capsules of lactose. It was not considered justifiable to run lactose controls in the cases of patients with severe exacerbations. Any advantage of antibiotic treatment was not statistically significant for patients with mild attacks of bronchitis.

Solanine Poisoning.—A small family outbreak of solanine poisoning was reported by G. S. Wilson (*Month. Bull. Min. Health* 18:211, 1959). A hotel proprietor and his family of four had cold meat with baked potatoes for supper. Four members of the family ate the skin as well as the pulp of the potatoes, and all suffered from food poisoning. The proprietor, who ate only the pulp, remained well. Two members of the family ate one potato and suffered slightly; one ate two potatoes and suffered more severely; and the fourth, who ate three potatoes, suffered acutely. Symptoms appeared about eight hours after the meal and consisted of vomiting, abdominal pain, diarrhea, and general malaise. All recovered within 24 hours.

The potatoes, which had been imported from Israel, were of excellent flavor and appearance and showed no evidence of sprouting. They were part of a stock of potatoes that had been used in the hotel for several weeks, but those used in the hotel had been peeled before cooking. Analysis of the potatoes revealed that they contained 50 mg. of solanine per 100 Gm. This was 6 times as much as was found in a sprouted green potato and 20 times as much as was found in potatoes purchased locally. As the average content of solanine in potatoes is generally about 8 mg. per 100 Gm. and the toxic dose for man as 20 to 25 mg., it is considered that the illness suffered by these patients was due to solanine.

The solanine content of potatoes is higher in, and immediately beneath, the skin than in the pulp. As solanine is diffused by boiling, but not by baking, the baked potatoes eaten with their skins caused illness. A review of the literature has revealed that the last notable outbreak of solanine poisoning in this country was in Glasgow in 1917, when 61 persons in 18 families were involved and one died. The solanine content of the potatoes from the household in which the death occurred was 41 mg. per 100 Gm.

Triethylene Melamine for Cancer.—Results obtained with triethylene melamine in the treatment of 43 patients with advanced inoperable lung cancer were reported by Gordon D. Jack and coworkers (*Lancet* 1:206, 1960). Thirty patients showed subjective improvement, and 10 showed marked to complete regression of the tumor. In four patients roentgenograms of the chest showed a return to normal or near normal findings. Treatment of these patients consisted of one or two large doses of triethylene melamine given intravenously (a total dose of 15 to 30 mg.). Within three days subjective improvement was evident, and on the fifth day routine roentgenograms of the chest showed evident shrinkage of the tumor mass. This shrinkage continued during the next three weeks, and at the end of a month the roentgenographic appearance had returned to normal. The patients were given 100 mg. of pyridoxine intramuscularly once daily and 50 mg. of dimenhydrinate (Dramamine) every six hours for nausea. A combination of reserpine and serpentine helped to restore a more than normal appetite by the fifth day of treatment. The pancytopenia was manageable with prednisolone and penicillin and occasionally blood transfusion.

Professor Chain Returns.—Professor E. B. Chain, who shared the Nobel Prize with Sir Alexander Fleming and Sir Howard Florey for the discovery of penicillin, is to return to London from Rome, where for the last few years he has been director of the Istituto Superiore di Sanità. This is a result of a grant of $980,000 from the Isaac Wolfson Foundation for the building and equipment of laboratories for biochemistry and chemical microbiology in the Imperial College of Science and Technology. With the announcement of this grant it was announced that Professor Chain has been appointed by the University of London to the chair of biochemistry. The Wolfson Laboratory will include large fermentation units and workshops for advanced mechanical and electronic equipment. Adequate accommodation is to be provided for training and research in those subjects that lie between biochemistry and chemical engineering.

Reform of the National Health Service.—Dr. J. G. M. Hamilton (*Brit. M. J.*, supp., Jan. 23, 1960) presented three major recommendations for the National Health Service: (1) a system of payment by item of service for general practitioners, modified perhaps by an element of salary inducement in certain appropriate circumstances, (2) administration by public corporation or corporations with medical preponderance and financed, especially in respect of hospitals, on the model of the University Grants Committee, plus insurance, and (3) a law to establish a physician's sole responsibility for his work.

Drug Addiction.—Addiction to narcotics has never been a serious problem in the United Kingdom, where there are only about 400 known addicts, most of whom are under police surveillance. The stress of modern life has produced a lesser type of addiction in those unable to face the realities and responsibilities of life. These people seek refuge in sedatives and tranquilizers, the continued use of which may lead to habituation. Some of these drugs are still obtainable without a prescription. Reports that two of them, carbromal and bromisovalum, could cause habituation and physical and mental deterioration caused the Ministry of Health to approach the Poisons Board to see if these drugs could be brought under control. The board reported that as these drugs were not poisons their sale could not be controlled. The drugs are constituents of a number of proprietary preparations that, until recently, were extensively advertised to the public for the relief of a number of mild ill-defined conditions. The Pharmaceutical Society, however, requested pharmacists not to supply such drugs without a prescription.

As the Poisons Board would not act, the Ministry of Health appointed a committee under the chairmanship of Sir Russell Brain, former president of the Royal College of Physicians, to investigate the matter and make recommendations. The committee's interim report (Drug Addiction, Interim Report of the Interdepartmental Committee, 1960, Her Majesty's Stationery Office, London) stated that habituation to carbromal and bromisovalum was infrequent but nevertheless serious in those in whom it occurred. The report stated that these drugs are merely examples of a variety of drugs acting on the central nervous system. They are freely obtainable from the drug store and may be dangerous if used injudiciously. Drugs of this type are often first obtained with a doctor's prescription, and the patient continues to use them without medical supervision.

The committee warned that the injudicious use of such drugs, and in fact all drugs acting on the central nervous system, could be dangerous to a person and to the community. It suggested that the drug be obtained only with a physician's prescription, and recommended that an independent expert body should be responsible for designating other preparations which should be supplied to the public only on prescription.

Anginal Syndrome.—Great success has been claimed for iproniazid in the treatment of the anginal syndrome, but its use for this purpose has been largely abandoned in Britain due to serious side-effects. Mackinnon and co-workers (*Brit. M. J.* 1:243, 1960) used pheniprazine to treat a series of 28 patients with the anginal syndrome. The severity of symptoms was carefully assessed beforehand. Because of the possible potentiation of pheniprazine, patients were instructed not to take barbiturates or tranquilizers during the trial. Six milligrams was given twice daily, and lactose tablets were given during the control period. In 12 patients improvement occurred with pheniprazine alone, and no benefit was derived from the placebo. Improvement, which normally began toward the end of the first week of treatment, was often dramatic, and most patients were able to discontinue trinitrin therapy. In some, improvement was delayed for 14 days. The maximal effect sometimes did not occur for three weeks. Only one patient improved with the placebo alone; 12 improved with both tablets. A total of 24 patients improved on pheniprazine therapy, and 13 improved on taking the control tablet. The improvement in individual patients was described as striking, although those conducting the trial admitted the difficulty of evaluating any drug used for the treatment of angina of effort. They suggested an extended trial of pheniprazine.

Iron Absorption and Steatorrhea.—In idiopathic steatorrhea and celiac disease, iron is absorbed poorly even in the presence of gross iron deficiency. Conventional treatment with a high-protein, low-fat diet and vitamin and mineral supplements does not improve the absorption. Recently, corticosteroids and a gluten-free diet have been introduced for the treatment of these conditions. They improve the absorption of fat and other substances, and it has been assumed, but never proved, that iron absorption also improves because the hemoglobin level is usually increased.

Badenoch and Callender (*Lancet* 1:192, 1960) examined the effect of giving cortisone, prednisone, ACTH, and a gluten-free diet to patients with idiopathic steatorrhea and celiac disease. Radioactive iron (Fe^{59}) was used as a tracer. Normal control subjects showed no change in the amount of Fe^{59} appearing in the red blood cells after treatment with 40 mg. of prednisone daily. Patients with steatorrhea who were treated with cortisone or prednisone showed an increase of between 17.5 and 55% in their absorption of iron. After a gluten-free diet had been followed by the patient the absorption of iron was usually, but not always, increased, and if the increase occurred, it was not as great as after treatment with corticosteroids. The defect in iron metabolism in steatorrhea seemed to be one of absorption, as parenterally administered iron was utilized normally. This suggested that the beneficial effects of corticosteroids and a gluten-free diet were due to a direct action on the intestinal wall. Corticosteroids may exert a beneficial effect on iron absorption in celiac disease and idiopathic steatorrhea by suppressing an abnormal antigen-antibody reaction.

Lung Function Studied with Radioactive Oxygen.—Dyson and co-workers (*Brit. M. J.* 1:231, 1960) devised a method of assessing regional variations of ventilation and blood flow in the lungs without intubation by using a radioactive isotope of oxygen (O^{15}). This method has advantages over bronchospirometry, which has been used to compare the function of the two lungs, as the latter method is unpleasant, not physiological, and does not measure local variations of function in the lungs. O^{15}, with a half-life of 2.5 minutes, decays with the emission of positrons, which are annihilated almost immediately by combination with electrons in surrounding matter, and with the production of gamma rays. By aligning scintillation counters in front of and behind the chest, the radioactivity of the O^{15} can be measured by counting the gamma rays that arise from cores of lung tissue between the counters. If two pairs of counters are used, the radioactivity of two regions can be measured simultaneously.

In the usual test the patient is given a single breath of air containing a trace of O^{15}. He then holds his breath for 12 seconds. Normally, the counting rate from any region increases rapidly to an initial peak, decreases slowly while the patient holds his breath, and decreases rapidly when the gas is washed out by subsequent breaths of room air. Because of the short half-life of O^{15} the test may be frequently repeated. Measurement of the initial activity allows the relative ventilation of two regions to be compared, and simultaneous records indicate the time relationship of the ventilation of these regions. The decrease in counting rate per second during holding of the breath is defined as the clearance rate which measures the uptake of O^{15} by the blood and is used to assess regional blood flow. The O^{15} test does not measure the function of a definite anatomic lobe or segment, which can be done at bronchoscopy by regional sampling of expired gas. The radiation hazard of the method is negligible because of the short half-life of O^{15}.

CORRESPONDENCE

ACCIDENTAL POISONING

To the Editor:—Some of the statements in the excellent article from the New York City Poison Control Center by Dr. Harold Jacobziner in THE JOURNAL, Nov. 28, 1960, page 1769, need further discussion. First of all, the cases reported to the Poison Control Center represent only a small proportion of all cases of accidental poisoning incurred by children in New York City. A study by Dr. Paul Wehrle and others from the Upstate Medical Center of the State University of New York at Syracuse indicates that the actual incidence of poisonings is probably close to 50,000 cases per year in New York City for persons under 20 years of age, although about 3,300 cases per year were reported in the period of Dr. Jacobziner's study. It is quite possible to make generalizations from a small sample if it is properly chosen, but Dr. Jacobziner's sample may have some large biases in it which would account for his preponderance of cases from lower socioeconomic groups. Data from Syracuse and our own data from a survey in San Jose indicate that the likelihood of accidental poisoning is evenly distributed throughout all social groups in a population. An exception to this might be the cases of lead poisoning.

Another indication of the selectivity of the cases reported to the New York City Health Department is the large number of patients (25%) admitted to hospital inpatient services. Experience in San Jose, where the Health Department has reports on a more typical cross-section of patients, indicates that the percentage requiring hospitalization is probably closer to 1%. The item which disturbs me most is the statement that "the value of a home visit by an experienced public health nurse cannot be overemphasized." Presumably the value of a visit from a public health nurse would be to prevent a subsequent poisoning or to reduce accidents or illness in a family with greater than average needs. There are no data in this report regarding the likelihood of repeating accidental poisoning in a family once it has occurred and none indicating whether or not families such as these are more apt than similar families to have accidents or health problems. Unpublished data from a survey which we have done indicate that families which have a child who experiences accidental poisoning are no more apt to have a high rate of accidents than the average of similar families.

Dr. Jacobziner states that "many of the families interviewed were unaware that the agents involved were hazardous, nor were they aware of practices used in the storage and handling of products." It is not clear whether they were unaware before or after the poisoning. It seems unlikely that they would persist in their naïveté after a case of poisoning, unless no effort whatsoever was made at the place of treatment to interpret the seriousness of the event. The only concrete evidence, therefore, that Dr. Jacobziner presents for the value of the public health nursing visit is that he thinks the families are receptive to safety education. Such use of public health nursing must be evaluated against the background of other priorities. Aside from receptivity, it might be argued that a public health nursing visit to prevent poisoning or other accidents might be made just as profitably to any group of families of the same socioeconomic status, with a child of the same age, etc., chosen at random.

If accidental poisoning is to be controlled, the opportunities available to physicians and health departments must be more effectively used. Systematic surveys of dwelling units, particularly apartment houses in older sections where lead paint is used, might be made by health department sanitarians. A one-year birthday reminder giving information about poison prevention might be mailed or presented in person by public health nurses to families. Broad-scale public education of the type Dr. Jacobziner mentions through press, radio, and television seems particularly inappropriate in dealing with a problem in such a restricted risk group. Considering the widespread nature of this problem and the number of near misses in addition to the high incidence of actual ingestion, one could argue that the primary reporting document for this condition is the birth certificate delivered by the physician or hospital to the health department.

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The above comment was referred to the author of the article cited, and he has submitted the following reply.

To the Editor:—I thank Dr. Bissell for his remarks. He says that there is a suggestion of bias and selectivity in my report. This comment is difficult to understand since the study included all reported poisonings to the center since its establishment in March, 1955—a total of 23,862 incidents. It was not stated or implied that it represented all occurrences; on the contrary, on numerous occasions we previously stated that many incidents are unreported. Though reporting of incidents has been mandatory in New York City since 1935, it was negligible prior to the establishment of the Poison Control Center, the number not exceeding 100 annually. In the first nine months of operation of the center, however, 2,908 incidents were reported. The number was 5,208 in 1956; in 1957 it was 7,247; in 1958 it rose to 8,499; and in 1959 the number exceeded 10,000. This does not mean that more incidents have occurred but that because of our educational efforts and the services which we provide reporting has improved. Actually we believe that the number of occurrences has been reduced. From 1950 through 1955 the annual number of deaths due to accidental chemical poisonings ranged between 111 and 130; in 1955 it was 120; in 1956 it was 81; in 1957 it was 70; and in 1958 it was reduced to 63.

We believe that ours is a representative sample without much bias or undue selectivity. Dr. Bissell states that the bias in our sample may also account "for the preponderance of cases from lower socioeconomic groups." While no ethnic, social, or religious group was exempt, a higher frequency was found in lower socioeconomic population groups. Over 40% of the families in which accidental poisonings occurred were receiving direct services from the Department of Health while only 33% of the city-wide population were receiving such services. Dr. Bissell points to the selectivity of our patients as judged by the large percentage admitted to hospital inpatient services, whereas the actual percentage requiring hospitalization in San Jose is probably closer to 1%. We merely reported what happened and not whether they required hospitalization. Communities will naturally vary with regard to hospitalization practices. With increased availability, there is probably a greater frequency of hospitalization.

Dr. Bissell is disturbed by the statement that "the value of a house visit by an experienced public health nurse cannot be overemphasized." We find such a visit most valuable, primarily because it tends to prevent future occurrences and alerts families to the importance of safety when they are apt to be most receptive. The public health nurse was able to help the family with other specific public health problems in more than 51% of the cases. A public health nurse's visit is also rewarding in obtaining additional epidemiologic data which are frequently lacking on the reports submitted by physicians and hospitals. Another effect is that the nurse picks up the actual sample of the incriminated product. This affords an opportunity to study defects in labeling or packaging and provides a basis for recommendations relating to corrective measures. The nurse's home visit is particularly helpful in the large number of suicides attempted by adolescents with chemical means, not only for obtaining accurate information but more importantly for insuring needed psychiatric follow-up examination to prevent future attempts. The visit is also an excellent device for inservice training of public health nurses in safety, accident prevention, and in making her more safety conscious.

Dr. Bissell is correct about the general lack of safety education provided at the place of treatment. I agree that each community must determine how best to use nursing time. In New York City, the Health Department believes in home visiting and feels that it is exceedingly rewarding, though because of shortage of time not all patients are visited. I agree about systematic surveys of dwelling, particularly with regard to prevention of lead poisonings. A sanitarian visits all places where an accident has occurred, and a year ago we recommended that sanitarians make a house-to-house survey in areas of high risks. I do not understand the basis for Dr. Bissell's comment that broad-scale public education of the type recommended by us is inappropriate. The fact remains that after every television showing, radio broadcast, and article in daily press and magazine we receive numerous written requests for information and advice and many telephone messages and letters of thanks for the help provided. After every attempt more persons and groups become involved in initiating safety programs. I do not know of any activity in the Department of Health which has received more appreciation from the medical profession and public alike.

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BLEEDING AND CLOTTING TIMES

To the Editor:—After reading the editorial, "Bleeding and Clotting Times," in The Journal, Jan. 2, page 63, I am prompted to follow Al Smith's slogan: "Let's take a look at the record." Is it true that "the ensuing 40 years of research brought not a clarification of the subject (theories of coagulation) . . .?"

Thirty years ago, when I was an intern at Blockley, Dr. Eldridge Eliason was called in consultation to see one of my patients who had extreme jaundice. He remarked: "If I don't operate she will die, and if I do operate she will probably die from postoperative bleeding." That was the era when blood clotting theories were simple, and only a few terms like antithrombin and antiprothrombin confused the medical student. After Drs. Bancroft, Stanley-Brown, and I (*Am. J. M. Sc.* 190:501 [Oct.] 1935) showed, by a simple method, the one-stage prothrombin time, that the prothrombin activity was often decreased in obstructive jaundice and later suggested that this was probably caused by a defective absorption of vitamin K (*J. A. M. A.* 109:66 [Oct. 16] 1937), cholemic bleeding soon shared the fate of the dodo. The importance of these developments has been voiced by various European investigators with statements such as "the one-stage prothrombin time opened a new era in blood coagulation research."

Prior to 1947, the coagulation defect in hemophilia was a complete enigma. Some investigators held that the defect was due to the slow liberation of thromboplastin from the platelets and others that it was caused by a lack of a plasma factor that was activated by contact with a foreign surface.

With the simple prothrombin consumption test (*Am J. M. Sc.* 214:272 [Sept.] 1947), it was possible to show that platelets contained an insignificant amount of thromboplastin but that they reacted with a plasma factor to form thromboplastin. This plasma factor was found to be lacking in hemophilia, which causes the poor prothrombin consumption in this disease. While it was subsequently shown that other factors are also essential in the formation of intrinsic thromboplastin, the basic concept of thromboplastin generation during coagulation was established in 1947. By means of the prothrombin consumption test modified by the addition of a new clotting factor (erythrocytin) obtained from erythrocytes, the hemophilic factor (thromboplastinogen, or factor 8) can now be quantitatively determined even for concentrations less than 0.1% of normal (Quick and Hussey: *A. M. A. Arch. Int. Med.* 97:524 [May] 1956). While all this has not brought about a cure for hemophilia, it has at least indirectly helped to improve the management of hemophilia. When I reviewed the literature for my monograph in 1942 (Hemorrhagic Diseases and Physiology of Hemostasis, Springfield, Ill., Charles C Thomas, Publisher.), it was most discouraging to read repeatedly: "Few hemophiliacs live beyond the age of five years." In my recent book (Hemorrhagic Diseases, Philadelphia, Lea & Febiger, 1957), I could state with assurance: "Even now, few hemophiliacs die from bleeding."

Certainly the results of these advances in the control of patients with bleeding diseases should well repay the medical student for having to study a little harder "to give coherent answers to examination questions on theories of coagulation."

I fully agree with the attitude expressed in the editorial on the routine use of clotting and bleeding times. Recently, I have critically evaluated the clotting time as a measure of hemostasis and have pointed out its great limitations (*S. Clin. North America,* 38:1031 [Aug.] 1958).

One should not fall into the error of making semantics the scapegoat for the present confusion. There are far more cogent causes. One of these is the error of regarding the clotting time as being synonymous with physiological coagulability, and another is the tenacious clinging to the myth that bleeding is stopped by a mechanical fibrin plug and that if the plug is formed too slowly, abnormal bleeding ensues. The greatest cause of confusion, however, is the lamentable state of our laboratories. Rarely can a new test be successfully introduced unless a commercial concern provides not only the reagents in a ready-to-use form but also the directions for carrying it out. The thromboplastin used in many hospitals for the prothrombin time is often not determined by the merit of the product but by the efficiency of the salesman. It may be true that "current physiological knowledge does not suffice to explain the differences between bleeders and nonbleeders," but if the knowledge that has already been developed were used, a little of the precision that is mandatory in the operating room introduced into the laboratory, and less dependence placed on mechanical gadgets, most bleeders would be recognized by means of the tests now available and many nonbleeders would be spared the anguish of being labeled bleeders because of the occasional bruise or nosebleed, especially during the season when the humidity in our living rooms approaches zero.

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RESEARCH AND COMMON SENSE

To the Editor:—I am motivated to comment on Dr. Beecher's article entitled "Research and Common Sense in a Clinical Specialty—Anesthesia" in the Jan. 30 issue of The Journal because misdirected articles by "big names," like misdirected bright lights, can too often be blinding. Dr. Beecher has made the common mistake of the false premise in his definition of "science" and has arrived at the false conclusion that "there is no science of anesthesia." His indictment, by his definition, includes all of clinical medicine. He was speaking of "pure science," but he denies the applied sciences. They are interdependent. One looks to the other for problems and solutions. His demand for well controlled research is backed by all.

It is sad to read Dr. Beecher's disparaging remarks about his specialty, anesthesia. His puristic view reminds one of that of a fragrant rose that would attempt to deny its roots the care and even the impure manure which was needed to bring it to fruition. Dr. Beecher's present opinion about the science of anesthesia is similar to that described by an 18th century poet who wrote:

> I loved thee beautiful and kind
> And plighted an eternal vow:
> So altered are thy face and mind
> 'Twere perjury to love thee now!

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COUNCIL ON LEGISLATIVE ACTIVITIES

HISTORY OF THE A. M. A.'S LEGISLATIVE ACTIVITIES

Introduction

The A. M. A.'s interest in legislation affecting the public health has existed since the first meeting of the Association in 1848 when it memorialized Congress to enact legislation providing for the appointment of inspectors at ports of entry to examine imported drugs and medicine. Shortly after this action, on June 26, 1848, Congress enacted a law to prevent the importation of adulterated and spurious drugs and medicine. Although the Association passed other resolutions concerning legislation and occasionally appointed special committees in connection with specific proposals, it was not until 1898 that the formation of a permanent legislative committee was suggested to the House of Delegates.

Throughout its history the Association has consistently believed that the medical profession has a duty to express its views on medical legislation both through its national organization and at the "grass roots level." The legislative conference held in St. Louis on Oct. 2-3, 1959, for state key legislative personnel was similar to the National Legislative Conference held by the first Committee on Legislation. The requests of present-day A. M. A. officials that physicians communicate with their congressmen are reminiscent of President Reed's statement in 1901 that "Every physician should in a perfectly respectable sense become an active, working politician. . . ."[1]

In the 61 years that have followed the creation of a Committee on Legislation there has been a tremendous growth in the amount of legislation affecting the public health and the medical profession. There has also been a growth in the number of medical societies and physicians. Although increase in the volume of medical legislation and membership have caused many changes in the mechanics of carrying out the Association's policies, its fundamental principles and main procedures have remained the same.

First Steps in Legislative Organization

The A. M. A.'s interest in uniform sanitation laws created an interest in the formation of a Committee on Legislation. In 1898 it passed a resolution to the effect that the need for such laws required the establishment of a National Department of Health. An editorial in The Journal[2] commented:

> Resolutions are all very well in their way, but it is questionable if they will have as telling an effect on a vote of the United States Senate, as an argument by individual members of the Association to individual members of the Senate.

The desire for a Department of Health and worry over an antivivisection bill introduced in the Senate are credited with the proposal for the formation of a National Committee on Legislation at the June, 1898, meeting of the House of Delegates. The proposal was referred to the Business Committee which rejected it saying that the Committee could not "see its way clear to the efficient operation of such a Committee without a considerable expenditure. . . ."[3]

However, the proponents of a legislative committee were not easily discouraged. In 1899 they introduced an amendment to the A. M. A. Constitution providing for a standing committee on legislation. Since there was a one-year waiting period for the establishment of standing committees, a resolution proposing an interim Special Committee on National Legislation was also made. Both proposals were adopted. Three members were appointed to the Special Committee and it was granted an appropriation of $250. The Committee was to have one member living in Washington, one in Baltimore, and one in Philadelphia in order that they could appear before Congressional Committees on short notice.

At its first meeting the Committee decided to call a Conference on Medical Legislation to which all the state societies were requested to send representatives. Invitations were also sent to the surgeon generals of the Army, Navy, and Marine Hospital Services. The Conference, which later became known as the National Legislative Council, was held in Washington, on May 1-2, 1900. Its agenda included a discussion of (1) the establishment of a Federal Department of Health; (2) publication of Index Medicus; (3) antivivisection legislation; (4) unification of medical practice acts; and (5) other medical legislation.

It was suggested that official sessions at the Conference be held in the afternoons so that the delegates could spend the mornings informing their respective Congressmen of their attendance at the A. M. A. Conference. The advantage of this procedure was that "the Committee would then represent in the minds of Congressmen not merely the

A. M. A. but the organized medical profession of the United States. . . . This move of the A. M. A. makes it possible for the opinions of the medical profession to exercise a steady pressure on Congress for the public good."[4]

By the time of the Conference the antivivisection bill had been defeated, and it was decided to concentrate on supporting three bills which would have improved the position of physicians in the Army. These legislative proposals concerned an increase in the number of physicians in the regular army, the creation of a medical reserve program, and the equalization of leave of absence and sick-leave benefits of assistant surgeons with those of other officers. The A. M. A. wished to raise the status of military physicians, feeling that their inferior status reflected badly on the status of civilian physicians as well.

A separate letter concerning each of the three proposals was sent to the Chairman of the House Committee on Military Affairs starting:

> We are directed by the Committee on National Legislation, which represents the American Medical Association and each state and territorial medical society of the United States, to inform you that. . . .[5]

Of the three bills only the one relating to sick leave was enacted into law.

At the request of the Surgeon General of the Marine Hospital Service the Conference also decided to support a bill which gave quarantine officers the power to arrest and administer oaths. A five-man subcommittee was appointed to write or visit Congressmen in support of the bill. It passed in the next session of Congress.

The Second Annual Conference on National Legislation was held in Washington on Feb. 20-21, 1901. Its most important achievement was the successful effort to influence legislation concerning second-class postal rates. The then existing law allowed weekly magazines to be mailed at the bulk rate of one cent per pound while newspapers and monthly periodicals paid one or two cents per copy. A commission appointed by Congress to revise postal rates proposed a bill which would have included the weeklies in the category of publications paying a per copy postage rate. The cost of distributing The Journal of the American Medical Association would have increased $30,000 a year if this bill had become law. When the conference discussed this bill they decided that the members should see their Congressmen personally. This decision was carried out, with the result that the bill did not reach the Senate floor.

A few years later the A. M. A. and its Committee on Legislation became involved in two important issues which were of vital importance to the public health. The first of these concerned the control of yellow fever and led to the Association's first battle with the executive branch of the government.

One of the main problems connected with building the Panama Canal was the death rate from yellow fever. The French company which started work at the Canal lost one-third of its non-native employees by death from this disease annually. When the United States became active in the project, the medical profession was seriously concerned about this death rate. In 1903 some of the state medical societies and the A. M. A. passed a resolution urging the President to appoint a physician to the Canal Council.

In 1904 the Conference on National Legislation urged the members of its Auxiliary Committee to request the President to appoint Col. William C. Gorgas to the Commission. The Auxiliary, which had been appointed the previous year, had given the A. M. A. 1,940 local representatives who would contact their Congressmen on medical legislation. Within 48 hours after the Auxiliary received a request for action, 1,400 telegrams arrived at the White House. Although the request for Gorgas' appointment was not granted, this demonstration of strength so impressed the Secretary of War that he overruled his Army Chief of Staff and granted the Conference's request that the Medical Corps have a seat on the Army General Staff.

Gorgas was appointed head of the Canal's Board of Health, but he had virtually no power and little progress was made in the war on yellow fever. In 1905 the Secretary of War sent the Chairman of the A. M. A. Committee on Medical Legislation to the Canal as a referee in a land value dispute. The Chairman was shocked to discover incredible delays in receiving medicine from the United States and other conditions which were blocking Gorgas' attempt to control the disease. On his return, he submitted a report of this situation to the American Medical Association. The report aroused a great deal of controversy and focused much interest on the problem of disease in the Canal. Although the Commission was reorganized shortly after the report and Gorgas was given more money, the Commission disagreed with his emphasis on mosquito control and tried to replace him.

The President, after consulting with the Chairman of the Committee on Legislation and other physicians who advised that Gorgas be retained, reversed the Commission and ordered them to cooperate with Gorgas. A year later, in 1907, malaria and yellow fever were well under control in the Canal Zone, and in 1908 Gorgas was finally appointed to the Canal Commission.

The A. M. A. and its legislation committee played a decisive part in the successful conclusion of this story. It has been termed one of the Association's greatest achievements in the field of public health.[6]

At the same time it was engaged in trying to improve health conditions in the Panama Canal Zone, the Association was fighting for health protection in the United States. Although the battle for the passage of a Pure Food and Drug Act had been going on for many years before the Committee on Legislation voted to actively support such a measure, the proponents had experienced little success in this effort. The A. M. A. did not believe it would be justified in fighting for the passage of the legislation until it was in a position to give helpful advice to the agency that would be in charge of enforcement if the bill was passed.

When the Council on Pharmacy and Chemistry was established and set up standards for testing drugs and related matters, the Association was ready for action. There were several groups besides the A. M. A.—the national magazines, the Federated Women's Clubs of America, and the Consumers League—who were in favor of a food and drug law. However, they were up against an old and powerful lobby, the whisky trust, which had kept this type of legislation "bottled up" in committees for years. In the summer of 1905 the aforementioned groups and the newly created National Pure Food and Drug League banded together and attempted to arouse public interest in the subject. Throughout that year many physicians, including the Chairman of the Committee on Legislation, urged the President to support the bill. In his State of the Union Message in December, the President indicated his support by asking Congress for a Pure Food and Drug Law.

In spite of the fact that public opinion and the President were behind the legislation, some Senators were determined to let it die in Committee. The Chairman of the A. M. A.'s Committee on Legislation told Senator Aldrich, an opponent of the bill, that he had some 135,000 physicians in back of him, "all organized locally into about 2,000 county units, each member instructed not only to act himself but to ask his patients and friends to bring pressure on the Senate."[7] A few weeks after this conversation the Senate passed the bill voting 63 to 4 in favor of it.

A monograph on lobbying has given the A. M. A. major credit for the passage of this measure:

> Although there were other factors aiding in securing the passage of the bill in the Senate, it cannot be doubted that the influence exerted by the American Medical Association and its followers was chiefly responsible for winning over the Senators. The Senate had maintained its opposition . . . for seventeen years and had it not been for the lobbying of the American Medical Association there is no telling how or when the lobbying on the other side would have been overcome.[8]

Even with passage of the Senate bill, the difficulties of the Pure Food and Drug Law were not over. It became stalled in the House of Representatives while efforts were made to compromise the House and Senate versions of the bill. To expedite matters the Committee on National Legislation prepared, for presentation to Congress, a petition urging the bill's approval. When the bill came to a vote on June 23 it was passed by a large majority, and on June 30, 1906, it was signed into law.

In both of these imprortant matters, the yellow fever problem and the need for food and drug legislation, the Association realized that action should be taken by organized medicine on both the national and the local level. By following the story of the solution to these two problems it is easy to see the importance of well-organized presentations of voter opinion to legislative representatives.

Further Expansion of Activities

The establishment of a federal department of health which had been on the agenda of the first National Legislative Council continued to be an important legislative objective of the A. M. A. and its Legislative Committee. Although it was many years before this effort became a reality, the constant efforts of the Association were undoubtedly in large measure responsible for the creation of this important federal department.

Another item on the agenda of the first Legislative Conference in which the A. M. A. continued to show interest was the preparation of a uniform medical practice act. The House of Delegates authorized a general conference to discuss the essentials of such an act in 1909. The conference, which was held early the next year, was attended by the Committee on Medical Legislation, the Council on Medical Education, members and officers of state medical boards, members of state committees on medical legislation, and representatives of medical colleges. The conference appointed a committee to formulate a uniform medical practice act. Prior to this time the Bureau of Legislation, which was established at A. M. A. headquarters in 1905, had been working toward the formulation of a model medical practice act.

The A. M. A. also showed interest in securing the enactment of laws relating to the use of narcotics. The Council on Health and Public Instruction, with which the Committee on Legislation merged in 1909, actively participated in hearings on the proposed Harrison Narcotics Act and also drafted some of its provisions.

Although the tax imposed on physicians under the Harrison Act was originally one dollar, it was increased to three dollars in 1918. The A. M. A.'s protests in this regard through the Bureau on Legislation were finally heeded in 1926, when the tax was reduced to its original amount.

The Association's interest in narcotics legislation was not limited to federal law. At the suggestion of the Bureau on Legislation, the Commissioners on Uniform State Laws formulated a model state narcotic law. The Bureau also assisted in the preparation of this model legislation.

Post World War I and Depression Years.—In 1924 Congress passed the War Risk Insurance Act, which provided hospitalization privileges for indigent war veterans with non-service-connected disabilities. This was the beginning of the government's program for non-service-connected disabilities, which the A. M. A. has opposed for 35 years. Although a Committee on Legislative Activities was appointed in 1930 to direct the activities of the Association's Bureau on Legislation it was later thought desirable to appoint an Auxiliary Committee to concern itself primarily with veterans' legislation.

This Auxiliary Committee had numerous meetings with the American Legion and the Veterans' Administration in connection with the treatment of veterans for non-service-connected disabilities. The Committee on Legislative Activities and other committees of the Association have been interested in other areas of veterans' legislation besides the one previously discussed. Presumptions of service connection, the adequacy of care for veterans afflicted with service-connected disabilities, and medical treatment for dependents of service personnel are only a few of the problems concerning servicemen in which the Association has maintained a continuing interest.

Other legislative interests in the 1930's included work on a proposed new food and drug law which was finally passed in 1938. Careful watch was also kept on the proposed Social Security Act. The initial bill proposed "to alleviate the hazards of old age, unemployment, illness, . . ." When the bill became law there was no reference to illness and a proposal that the Social Security Board make recommendations with respect to health insurance was eliminated.

World War II.—During the war, most of the Association's activities were directed toward helping the national war effort and there was not much emphasis placed on legislative activities. The first Wagner-Murray-Dingall National Compulsory Health Insurance Bill was introduced during this period and was vigorously opposed by organized medicine. However, this proposal did not receive great attention until 1948.

The Present.—From 1948 until the present time the Association has been in a continuous battle against the forces of socialized medicine. The primary emphasis from 1948 to 1951 was on opposition to a new version of the Wagner-Murray-Dingall bill. Although similar legislation is still being introduced, the emphasis has shifted since 1957 to a more limited objective, hospitalization and partial medical care for OASDI beneficiaries. Although the Association has been extremely busy educating the public and Congress concerning the dangers of this type of legislation, it has had numerous other legislative interests. The Council on Legislative Activities reviews several hundred bills during each session of Congress. The main legislative concerns besides socialized medicine have been veterans legislation, the Hill-Burton laws, retirement plans for the self-employed, and proposals affecting medical education and research.

During the last decade many steps have been taken to further improve the Association's activities in the field of medical legislation. In 1944 the request for a permanent Washington Office was adopted, and, in December of 1949, at the clinical meeting in Washington, the House of Delegates adopted the following report of the Reference Committee on Legislation and Public Relations:

> Since the Washington Office is now under the direction of the Board of Trustees instead of, as formerly, under the Council on Medical Service, in order to promote more effectively the activity of this office and implement its work, your reference committee recommends that the Board of Trustees appoint a committee of not less than seven members from the Trustees and general membership. The Committee's function should be the facilitating of the activities on legislative matters and the dissemination and distribution of legislative information throughout the various states. Your committee furthermore recommends that the Board of Trustees give immediate consideration to proper financing of this Committee, to permit adequate functioning in this field.

As a result of this action, the Board of Trustees appointed the Committee on Legislation, which held its first meeting in Chicago, Jan. 15, 1950. At this time the principal functions of the Committee were described as follows: (1) to streamline legislative action so as to get faster and more effective results in Washington; (2) to study and report on all legislation introduced; (3) to maintain knowledge of the current status of and take suitable action on all bills previously introduced; (4) to assure the dissemination of information to local and state medical societies with respect to current legislation and actions recommended; and (5) to recommend the names of physicians for the presentation of testimony to congressional committees.

The Committee adopted several procedures for carrying out its functions. One of these was periodic meetings at which it considered legislation of medical interest which was currently before the Congress of the United States. After careful consideration and study, the Committee adopted a position on each measure which it recommended to the Board of Trustees. In addition to these regular meetings, the Committee has conducted legislative conferences for key men and local medical society executives. Each committee member is also assigned several states in which it is his responsibility to disseminate information on current legislation.

The adoption of the "key man" system in 1957 has also improved distribution of legislative information to members of the A. M. A. Under this system, the Board of Trustees appoints one physician in each state who directs and is responsible for federal legislative activities in that state. Also in 1957 the Woman's Auxiliary was asked to appoint "key legislative women" in each state to do similar work.

At the December, 1958, meeting of the A. M. A., the Board of Trustees changed the name of the Committee to "Council on Legislative Activities." The Council's functions are substantially similar to those it had as a committee. One new activity which the Council has undertaken is the publication of a newsletter entitled *Medical Legislative Digest*. The newsletter which is issued at least twice a month while Congress is in session contains analyses of legislative proposals, status reports on pending bills, and other information of interest to physicians who have a special interest in medical legislation.

Appendix

Development of American Medical Association's Legislative Activities

1899—Interim Special Committee on National Legislation approved.

1899—Constitutional amendment establishing a standing committee on national legislation approved.

1900—First Annual Conference on National Legislation.

1901—New A. M. A. Constitution reaffirms status of National Committee on Medical Legislation as a standing committee.

1901-1902—Auxiliary Committee on Medical Legislation composed of one member from each state and territorial society represented in A. M. A. and one member of Army, Navy, and Marine Hospital services established.

1905—Establishment of Bureau of Medical Legislation at A. M. A. headquarters approved.

1911—Standing Committee on National Legislation merged with Council on Health and Public Instruction.

1927—One staff member of Bureau assigned to Washington while Congress in session.

1930—House of Delegates authorizes Speaker to appoint Committee on Legislative Activities.

1944—Washington office of A. M. A. opened.

1949—Board of Trustees appoints Committee on Legislation.

1954—Resolution passed suggesting that some mechanism be instituted to obtain attitude of each state medical society on pending federal legislation.

1954—Legislative newsletter for key legislative personnel instituted.

1957—Key legislative man in each state appointed to work with state medical societies and Committee on Legislation.

1957—Woman's Auxiliary asked to appoint key legislative women for each state.

1959—Committee on Legislation becomes Council on Legislative Activities.

1959—Council on Legislative Activities commences publication of newsletter, Medical Legislative Digest, for physicians with an active interest in national medical legislation.

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MEDICAL FILM REVIEWS

Second Chance: 16 mm., black and white, sound, showing time 30 minutes. Supported by a grant from E. R. Squibb and Sons. Produced in 1959 by George C. Stoney Associates, New York, for and procurable on rental or purchase from American Heart Association Film Library, 267 W. 25th St., New York 1.

This motion picture deals with some of the problems of caring for a stroke patient at home and emphasizes the benefits of beginning rehabilitation promptly. It is based on the case history of a 63-year-old fireman who fought and won a hard battle of rehabilitation after he had been paralyzed by a stroke. He reenacts the experience from the acute phase of the stroke to the point where most of his functions are restored. Detailed attention is given to physical problems of the stroke patient and to physical therapy techniques. The film deals frankly with emotional problems confronting the patient and his family. The story, one of hope, is told in a quiet, warm, and cheerful tone. It is excellent as a dramatic presentation as it anticipates and deals with the emotional problems of both the family and the patient. This is an excellent film, and the photography, production techniques, and narration are exceptionally good. Well planned scenes which contribute to the feeling of authenticity of the story help the motivational impact of the film. It is highly recommended for physicians to use to interest community groups in rehabilitation programs and to encourage the patient as well as his family to have the courage to face the problem and to expend the energy necessary to overcome it. A companion film entitled "Cerebral Vascular Disease: Challenge of Management" has been produced especially for professional audiences and was reviewed in THE JOURNAL, Jan. 23, 1960, page 370.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Experimental Laennec Type of Cirrhosis in Monkeys. G. F. Wilgram. Ann. Int. Med. 51:1134-1158 (Dec.) 1959 [Lancaster, Pa.].

After numerous failures with various abnormal diets on several cebus and rhesus monkeys, the author reports the successful production, by dietary means, of a Laennec type of cirrhosis in 2 male cebus monkeys. These 2 monkeys served as their own controls for a preliminary observation period of 1½ years, after which time they were given a cirrhogenic diet for 17 months. For 2 brief intervals during these 17 months they received a complete, nutritious diet to prevent death. The cirrhogenic diet was low in protein, free of choline, and rich in cholesterol (2%). A Laennec type of early cirrhosis developed in both animals.

After the diagnosis was established by laparotomy and histopathological studies, the animals were given a nutritious regimen as a therapeutic trial for 9 months. Portal hypertension, ascites, and icterus disappeared. The clinical condition of the animals and the gross appearance of their livers improved considerably, but the histological picture could not be restored to normal within that period. Serum protein determinations showed an inversion of the albumin/globulin ratio, which persisted despite proper therapeutic management and clinical rehabilitation. The data obtained were in keeping with the clinicopathological concept that cirrhosis is induced by a combination of etiological factors but not by any single cause. Equally important factors in the induction of cirrhosis are the nutritional state of the liver cells, hepatic injury, and the ability of the liver to repair inflicted damage by regeneration. The possibility has been considered that autoimmunization against liver-cell protein altered by injury may perpetuate the cirrhotic process, despite removal of all injurious factors, but this speculation requires further studies.

Familial Recurring Polyserositis: A Disease Entity. R. J. Priest and R. K. Nixon. Ann. Int. Med. 51:1253-1274 (Dec.) 1959 [Lancaster, Pa.].

The authors present observations on 20 patients with familial recurring polyserositis and review the literature. This entity is limited mostly to persons of Armenian, Syrian, or Jewish ethnic origin, and has been referred to as paroxysmal syndrome, paroxysmal peritonitis, periodic abdominalgia, periodic disease, Armenian disease, and familial recurring polyserositis. The patients have periodic episodes of severe abdominal, chest, or joint pain, with fever, leukocytosis, and physical signs corresponding to the particular serosal membrane involved, i. e., peritoneum, pleura, or synovia of joints. The meninges and pericardium may also become involved.

The presenting complaint is usually recurring paroxysms of severe abdominal pain. The temperature is usually elevated, varying from 99 to over 104 F (37.2 to 40 C), and leukocytosis is a frequent finding. Pleuritic pain may occur in some patients, or stethalgia may be associated with abdominalgia. The patient may flex his thighs to relieve the abdominal pain, and may resist any movement to avoid pain. Palpation of the abdomen elicits exquisite tenderness. During episodes of pain, most patients refuse nourishment, and may vomit. Patients recover from each episode of pain and are in normal health in the interval of weeks or months between attacks. The abdominal crises usually subside in 48 hours, and the majority of patients have learned to refuse unnecessary abdominal operations. Nevertheless, 14 of the 20 patients reviewed underwent 18 operations. The disease is a chronic one, which may first appear during infancy, but more frequently during the second or third decade.

The etiology and pathogenesis of this form of polyserositis are incompletely understood, but the authors feel that the disorder may be added to the list of those with an inborn error of metabolism. The hereditary nature has been established. A history of familial incidence was established in 5 of the 20 patients in this series, and some patients (because of wars and displacement) knew nothing of their family history. The seemingly interminable recurrences may involve these patients in serious economic and sociological problems, and it is hoped that further investigation of the disorder might provide relief.

The place of publication of the periodical appears in brackets preceding each abstract.

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Cystic Fibrosis of the Pancreas. A. M. Amundsen. Tidsskr. norske laegefor. 79:1356-1361 (Dec. 1) 1959 (In Norwegian) [Oslo].

Since 1938 more than 1,000 cases of cystic fibrosis of the pancreas have been described. Etiology and pathogenesis are far from clear. The disease is regarded as hereditary, due to dysfunction in the exocrine glands. Analyses of 141 families, published by 6 different authors, seem to show that the disease depends on a recessive gene. Between 2 and 18% of the population are thought to harbor this specific gene. The disease is known in many lands, is rare among Negroes, and has not been described among Mongolians. Pulmonary disease is its gravest manifestation. In most cases there is a combination of pancreas insufficiency and chronic pulmonary disease. The chloride and sodium concentrations in the sweat are from 2 to 5 times higher than in normal persons. Widespread disturbance of mucous secretion may affect many organs. Near relatives of patients with the disorder often have sweat anomalies. The picture may present marked variations. Diagnosis should be based on increased chloride and sodium values in the sweat, generalized obstructive emphysema and chronic bilateral pneumonia, absence of pancreatic enzymes in the duodenal juice, demonstration of the disease in near relatives, and, in rare cases, liver cirrhosis with hepatosplenomegaly and symptoms of portal hypertension. The pulmonary changes are in most cases decisive for the prognosis. In more than 90% of the cases death is ascribed to chronic pulmonary disease.

Treatment is directed mainly to the pulmonary symptoms and, in the second place, to the pancreas insufficiency. The importance of antibiotics in treatment of the pulmonary complications is generally accepted. Antibiotics are often given initially in large doses for 1 or 2 weeks. If there are pulmonary symptoms after this treatment, prophylactic doses of antibiotics with broad spectrum may be necessary for months and years. Dosage with antibiotics over a longer period involves the danger of development of bacterial resistance or fungous infection. Surgical intervention may be considered in cases with lobar atelectasis.

SURGERY

Radical Mastectomy for Carcinoma of the Breast. E. B. Gray Jr. and T. J. Anglem. New England J. Med. 261:1310-1314 (Dec. 24) 1959 [Boston].

A follow-up study on 184 patients with cancer of the breast treated by radical mastectomy is reported. One hundred fourteen patients were alive after 5 years (62% absolute survival); leaving out 12 indeterminate results, the 5-year survival was 66%. No evidence was found that any of the patients in the series were harmed by the operation. The authors believe that radical mastectomy is a more effective form of therapy for operable cancer of the breast than irradiation with or without simple mastectomy, although some local manifestations of advanced disease contraindicate the operation. These include the presence of supraclavicular metastases, fixed axillary lymph nodes, extensive edema of the skin of the breast, satellite skin nodules, inflammatory carcinoma, and chest-wall fixation. The authors believe that, with these exceptions, radical mastectomy should be used in carcinoma of the breast, so long as remote metastases are absent.

Diagnosis and Prognosis of Cauda Equina Syndrome Produced by Protrusion of Lumbar Disk. R. H. Shephard. Brit. M. J. 2:1434-1439 (Dec. 26) 1959 [London].

Thirteen of 139 patients who during a 6-year period were subjected to laminectomy were suffering from cauda equina compression. Diagnosis of the cauda equina syndrome can be made by evaluation of the history and by clinical examination. When such a lesion is suspected, judicious inquiry should be made for symptoms indicating compression of lumbar or sacral nerve roots. The most important of these are weakness of muscles below the knees, impairment of skin sensation in the saddle area, difficult micturition, and radiating symptoms. Radiating symptoms consist of pain, tingling and other paresthesias, or numbness. Constipation may go unnoticed if it represents little change in the patient's usual bowel habit. Examination will be directed especially toward the spine, the lumbar and sacral skin and muscle segments, and the bladder. The only way of examining the sacral segments adequately is with the patient prone. Even small degrees of wasting of the buttocks will be apparent; loss of tone, weakness of the gluteal muscles, and sensory loss in the sacral dermatomes can be readily demonstrated. One or both ankle jerks are absent in most of these cases. A distended bladder not uncommonly escapes casual observation.

The cauda equina syndrome is only very rarely complete—in disk cases, only the lower lumbar, sacral, and coccygeal roots are involved—and is often asymmetrical in regard to both right and left sides and to manner of involvement of "motor," "sensory," and "sphincter" supply. The most common, and remediable, cause of the syndrome is central prolapse of a lower lumbar intervertebral disk. In most such cases there is a long history of lumbar back pain—constantly or, more commonly, as attacks of lumbago—or radiating symptoms; there is often a back strain due to twisting or lifting, sometimes slight in degree and apparently trivial, immediately before the onset of the symptoms of cauda equina compression.

The number of patients in the series reported represent a high incidence relative to the total number of patients suffering from lumbar disk disease. The incidence is also high compared with other series. With regard to the association of manipulation and cauda equina syndrome, the author points out that such a maneuver precipitated the onset of the syndrome in one patient. If there is any evidence to suggest a central disk prolapse not yet producing a cauda equina syndrome, manipulation should be avoided. The finding at operation in a number of these patients of a thinned annulus and posterior common ligament, and the fact that so many of the frank cases of the syndrome follow relatively trivial traumas acting on an already diseased disk, indicate the danger of manipulation. The profound disturbance of function which follows acute central prolapse of extrusion of a lumbar disk is clear in the cases reported by the author. The slow return of this function, with delay in diagnosis and operation, is also apparent. These lesions do not of themselves endanger life. However, when no relief is afforded, the paralysis of bladder and sensory function leads to ascending urinary infection and decubitus ulcer formation, and so result in a shortening of the life span. Uremia or septic absorption from bedsores brings to an early end a miserable and limited existence.

Surgical Treatment of Pulmonary Stenosis and of Interatrial Defects. I. Perianes, E. Murga and E. Altmann. Prensa méd. argent. 46:1829-1832 (July 17) 1959 (In Spanish) [Buenos Aires].

Thirty-five patients with congenital heart disease were observed in the department of cardiology of the Hospital de Clínicas, Buenos Aires, between 1955 and 1959. Thirty-one patients were children, and 4 were adolescents. Twenty-three patients had pulmonary stenosis, and 12 had interatrial septal defects of the first, second, or fenestrated types. An operation was performed on all the patients with pulmonary stenosis and on 10 of the 12 with interatrial spetal defects. Open-heart surgery, with transient discontinuation of circulation in hypothermia, was used in the 23 patients with pulmonary stenosis and in 7 of the patients with interatrial septal defects; in the remaining 3 patients with interatrial septal defects, either Gross's semi-open-heart surgery with normal body temperature or open-heart surgery with extracorporeal circulation was used. The surgical approach was through a longitudinal or transverse sternotomy, followed by either a left or a right anterolateral thoracotomy according to the type of the lesion, either pure pulmonary stenosis of the valvular type or interatrial septal defect. The operation consisted of valvulotomy or of infundibulectomy in patients with pure pulmonary stenosis. There were no complications or operative mortality in this group. Permanent satisfactory results were obtained in 22 patients. One patient died 25 days after the operation of a mediastinal abscess involving the suture of the pulmonary artery. In patients with interatrial septal defects, the operation consisted of correcting the septal defect through the opened right atrium. Permanent satisfactory results were obtained in 9 patients. The only adolescent patient in this group had the operation with extracorporeal circulation. The interatrial septal defect in this patient consisted of a nearly complete lack of septum. The patient died in the course of the operation.

The authors conclude that open-heart operations give permanent satisfactory results in patients with pure pulmonary stenosis. The risks are not greater than those met with in closed-heart operations. Open-heart or semi-open-heart operations give permanent satisfactory results in the treatment of interatrial septal defects.

Acute Osteomyelitis Treated with Penicillin: Treatment and Results of Treatment Evaluated from the Literature and Personal Material of 307 Patients. M. Gerner-Smidt. Bibl. laeger 151:165-199 (no. 5) 1959 (In Danish) [Copenhagen].

Of the author's 307 patients, 296, with 305 cases of osteomyelitis, were followed up; 3 had died during hospitalization, 4 had died before the follow-up (only one of these of osteomyelitis), and 4 could not be traced. Clinical follow-up showed neither subjective nor objective symptoms in 239 cases (78.4%), mild periodic pain or small objective changes in 44 cases (14.4%), more marked pain or graver arthrosis or greater limitation of movement in 10 cases (3.3%), and grave changes in the form of ankylosis or large deformities requiring further therapy in 12 cases (3.9%). In about one-sixth of the cases there were roentgenologic changes in which a focus could not be excluded; in five-sixths of the cases recurrence should not appear. Patients with graver clinical sequelae constituted 7.2% of all followed up. Roentgenologic follow-up was carried out in 291 patients, representing 300 cases. The results showed healing in 206 cases (68.7%), focus only in 58 cases (19.3%), focus and deformity in variable extent in 22 cases (7.3%), and only some deformity in 14 cases (4.7%).

From the literature and the personal cases the conclusion is that penicillin seems to be the main factor in the modern treatment of osteomyelitis. More than any other therapy, penicillin can influence the mortality, bacteremia, general condition, temperature, and the disease itself. Sulfonamides exert a certain effect on the mortality and the pyemic metastases but no effect on the temperature and the local infection. The better effect of penicillin over sulfonamide preparations is explained only by the far greater sensitivity of staphylococci to penicillin.

Results of Surgical Treatment for Bronchial Carcinoma. A. E. Paletto, E. Masenti and F. Viglione. Chir. torac. 12:339-353 (Aug.) 1959 (In Italian) [Rome].

The authors report on 490 patients with bronchial carcinoma, who were treated at the Institute of Surgical Pathology of the University of Turin until the end of 1956. Resection which was performed in 143 patients consisted of extensive pneumonectomy on 31, simple pneumonectomy on 64, lobectomy on 45, and segmental resection on 3. There were 347 patients with inoperable disease. The inoperability was determined clinically in 278 patients and on thoracotomy in 69. Four patients (9.7%) who had undergone resection survived more than 5 years. Patients with epidermoid carcinoma tolerated the operation better and survived longer than patients with other types of carcinoma, such as adenocarcinoma or the undifferentiated type of carcinoma. Age per se did not significantly affect the survival chance in patients who had undergone resection; rather, the general state of health and the status of the cardiovascular and respiratory systems played an important role in the survival. The highest postoperative mortality rate was observed within 2 years after the operation. This may mean that the extent of many lesions in these patients has reached the limit of operability.

The authors believe in the surgical treatment of patients with bronchial carcinoma. Early diagnosis is the main aid to the surgical treatment whereby early lesions are discovered. Unfortunately the early lesions are frequently quite extensive. The authors suggest postoperative radiocobalt (Co^{60}) therapy in patients in whom mediastinal and pleural involvement was observed at the time of operation.

Femoral Bypass Grafts. E. J. Whitman, J. M. Janes, J. C. Ivins and E. W. Johnson Jr. Surgery 47:29-45 (Jan.) 1960 [St. Louis].

The authors report on 71 men and 3 women, between the ages of 40 and 60 years, in whom 96 femoral bypass grafts were inserted at the Mayo Clinic in the 3-year period ending October, 1958. Of these, 58 were homografts, 15 were Edwards-Tapp nylon grafts, and 23 were Teflon grafts. Seventy-six of the grafts were inserted in the course of surgical intervention for segmental occlusion of the superficial femoral artery in patients with arteriosclerosis obliterans associated with severe intermittent claudication; 7 grafts were performed for popliteal aneurysm; 1, for femoral aneurysm; 8, for regrafting after failure of homograft; and 4, for trauma to the femoral artery. Follow-up information was available concerning 91 of the 96 grafts. Of these, 43 were functioning grafts at the time of follow-up. Eighteen (78.3%) of the 23 Teflon grafts were functioning (Teflon is far superior to any other type of graft). Many patients who had grafts which occasionally failed had palliation for a considerable period before ultimate failure, some up to 32 months. There were no surgical deaths and little morbidity. Ten patients eventually had amputations, but more than one-half of these would have been required immediately if grafting had not been performed.

It is hard to judge from this study how many patients would have required amputation without grafting. Other patients who now have functioning grafts have undoubtedly been saved from amputation or have required only amputation of single gangrenous toes after grafting. These patients were in a productive age group, and intermittent claudication and manifestation of ischemia were a severe handicap to many of them. The results obtained suggest that, with proper indications, the use of femoral bypass grafts for occlusive disease of the femoral artery is worthwhile. In the authors' hands, Teflon is the material of choice.

An Assessment of the Value of Arterial Grafting. J. A. Key, W. G. Bigelow and E. P. Farber. Surgery 47:74-78 (Jan.) 1960 [St. Louis].

The authors report on 160 patients with chronic arteriosclerotic occlusive disease and on 77 patients with abdominal aneurysm, who were operated on at the Toronto General and Sunnybrook hospitals in Toronto. These patients were between the ages of 42 and 80 years, and the ratio of men to women was 4.5 to 1. Of the 160 patients, 97 underwent femoral arterial grafting, and 63, aortoiliac grafting. With few exceptions, the femoral grafts were all of the end-to-side bypass type. Forty-four were arterial homografts, and 52 were crimped nylon grafts; there was one autogenous vein graft. Of the aortoiliac grafts, 41 were homografts, and 22 were nylon prostheses. With one or two exceptions, the proximal anastomosis was of the end-to-end variety. The distal anastomosis was end-to-end in 28 patients, and in 35 it was of the end-to-side bypass type. A 3-year follow-up showed that the initial success rate in the 97 patients with femoral arterial grafts was high for either homografts or nylon grafts; 67.5% of these grafts were a complete success, and 17.5% were considered a partial success, an initial success rate of 85%. The early failure rate was higher with nylon grafts than with homografts. The late failure rate was higher with homografts than with nylon grafts. Of 10 patients with femoral occlusive disease who underwent grafting, the grafts were initially successful in 8, and in 5 they were satisfactory at the end of 3 years. The initial success rate in the patients with aortoiliac grafts was reasonably high for either homografts or nylon grafts. Complete success was achieved in 50.9%, and partial success in 24.5%, giving a total success rate of 75.4%. The early failure rate was higher with homografts than with nylon grafts. The late failure rate with homografts and nylon grafts was about the same. Of 10 patients with aortoiliac occlusive disease who underwent grafting, the grafts were initially successful in 7, and in 5 they were satisfactory at the end of 3 years.

These results suggest that arterial grafting is a valuable procedure, and at present there is no certain way of relieving intermittent claudication other than by a successful graft (or thromboendarterectomy); the ideal arterial graft substitute has not yet been found. Considerably better long-term results can probably be achieved by more careful selection of patients and by paying greater attention to the condition of the outflow tract.

Of the 77 patients with abdominal aneurysm, the aorta was replaced by homografts in 42 and by crimped nylon bifurcation grafts in 35. There were 3 patients with aneurysm occurring in the homografts, 2 of whom died after attempts to deal with this complication. In dealing with aortic aneurysm, the authors recommend that, if ruptured, immediate operation should be performed, giving the only real hope of continued survival of the patient. In patients with unruptured aneurysm producing symptoms, resection of the aneurysm should be considered as a relatively urgent necessity; and, if symptomless, the aneurysm should be removed as an elective procedure, provided that there is no major complication, that the cardiac and renal functions are satisfactory, and that the patient is not too advanced in years.

Evaluation of Late Failures After Reconstructive Operations for Occlusive Lesions of the Aorta and Iliac, Femoral, and Popliteal Arteries. E. S. Crawford, M. E. De Bakey, G. C. Morris Jr. and E. Garrett. Surgery 47:79-104 (Jan.) 1960 [St. Louis].

The authors report on 1,225 patients with occlusive lesions of the distal aorta and iliac, femoral, and popliteal arteries, who underwent reconstructive operations with a variety of arterial replacement at Jefferson Davis, Methodist, and Veterans Administration hospitals in Houston, Texas, during the last 6 years. Lesions were located in the distal aorta and iliac arteries in 638 patients and in the femoral and popliteal arteries in 587. The indications for operation were rest pain or intermittent claudication in 80% of the patients, and in the remaining 20% cutaneous lesions that posed an immediate threat to life. Endarterectomy, excision and graft replacement, and bypass were the procedures which were employed and adapted to the nature and extent of the occlusive process. Peripheral pulsatile circulation was initially restored in 96% of the 638 patients treated surgically for lesions of the aorta and iliac arteries. Thirty-eight patients (6.2%) had recurrent difficulties resulting from aneurysmal dilatation of the grafts, false aneurysm, aortoduodenal fistula, or recurrent obstruction. These complications are preventable with present knowledge of treatment of lesions in this location. Particularly noteworthy is the fact that circulation was successfully restored in 33 of the 38 patients who had a second reconstructive operation.

Peripheral pulsatile circulation was restored in 88% of the 587 patients on whom reconstructive operations were performed for occlusion of the femoral and popliteal arteries. The best results (91%) were obtained with the bypass procedure and a flexible, knitted Dacron graft. This procedure was employed in more than 50% of the patients in this group. The poorest results were obtained in the small number of patients treated early in the authors' experience by endarterectomy or excision and graft replacement. Late failure occurred in 109 patients (21%). Long-term functional results with the flexible, knitted Dacron tube inserted as a bypass graft were superior to those in which braided nylon or homografts were used. Most of these failures resulted from preventable complications; but circulation was restored in 58 (91%) out of 64 patients by reoperation. These data indicate that the immediate and long-term functional results of surgical treatment may be significantly improved by increasing surgical experience, better understanding of the underlying disease, improved methods of arterial visualization, and better graft material. In addition, aggressive treatment of late failures is usually successful.

Crepitation of the Scapula. E. Geyer. Ztschr. Orthop. 92:219-224 (no. 2) 1959 (In German) [Stuttgart, Germany].

The author found that in crepitation of the scapula French authors had differentiated the degrees of loudness into *froissement* (rustling), *frottement* (friction rub), and *craquement* (crackling). The first 2 degrees are generally perceptible only with the aid of the stethoscope and are largely physiological, whereas the *craquement* corresponds to the crepitation which exceeds the physiological limits. It is perceived by the patient and is often accompanied by pain.

Clinical examination reveals pain on pressure in the region over the median rim of the scapula, often at the upper inner angle or the rhomboideus muscles, and occasionally at the lower angle of the scapula. Roentgenoscopy is rarely informative, except in the case of gross scapular deformities, such as exostoses. While many explanations have been attempted, the etiology is still largely unexplained. Some investigators attributed the condition to friction resulting from incongruence of the sliding surfaces; others traced it to the subscapular bursae or to Luschka's knob at the upper inner scapular angle. At present painful scapular crepitation is believed to be caused by impairment in muscular coordination, and some cases remain unexplained.

The author presents a 27-year-old man of asthenic build, who complained of pain and crackling noises on movement of the right scapula. Various methods of physical therapy had been unsuccessful, and no definite anatomic cause could be established for the painful crepitation which had existed for about 5 years. It was assumed that a disturbance in muscular function was probably chiefly responsible. Healing resulted after surgical removal of the caudal angle of the scapula.

The Three Types of Acute Haematogenous Osteomyelitis: A Clinical and Vascular Study. J. Trueta. J. Bone & Joint Surg. 41B:671-680 (Nov.) 1959 [London].

The author reports on 202 patients with acute hematogenous osteomyelitis, who were treated at the Nuffield Orthopedic Center in Oxford, England. Of these, 162 (80%) were children (between the ages of 1 and 16 years); 14 (7%) were infants, aged less than 1 year; and 26 (13%) were adults. The observations in these 3 groups of patients confirmed that acute hematogenous osteomyelitis varies in its clinical characteristics according to the age of the patient. Thus, osteomyelitis of the infant, the child, and the adult constitutes 3 separate clinical entities with few features in common apart from the generalized, or septicemic, phase of the disease which was observed in all the patients. The 3 age types of the disease are conditioned in their respective clinical features by the differing nature of their vascular bone pattern. Vascular studies confirmed that the capillaries adjacent to the growth plate in its metaphysial side are, apart from a narrow fringe at the periphery of the plate, the last ramifications of the nutrient artery; these, after turning down in acute loops, reach a system of large sinusoidal veins responsible with others for the hematopoietic activity of the bone marrow. It is here that the blood flow slows down and that the pathogenic bacteria, particularly the coagulase-positive Staphylococcus aureus, find an ideal medium for development. The vascular barrier represented by the growth cartilage is first obvious at the age of 8 months and is definitely established before the 18th month, except for some peripheral vascular connections between the epiphysis and the metaphysis. Thus, from the point of view of the vascular anatomy, the infant becomes a "child" at the age of one year. By the progressive penetration of the growth cartilage by metaphysial vessels, its height is reduced until after the end of growth vascular connections are established between the epiphysial and metaphysial systems of vessels. From then on, the blood in the nutrient artery reaches the surface of the epiphysis through large anastomoses; thus, bacteria penetrating the nutrient artery may be brought to the vascular loops under the articular cartilage and spread the infection into the joint.

In the infant the condition causes severe and often permanent epiphysial damage and joint infection, a large involucrum, but only transient damage to the shaft and metaphysis. In the child the condition is responsible for extensive cortical damage with involucrum formation; it seldom causes permanent damage to the growth cartilage and to joints. On the contrary, in more than 30% of the children growth was stimulated by the increased vascularity of the metaphysial side of the growth plate. Chronicity of the disease is rare if treatment has been effective. In the adult, acute osteomyelitis of the long bones is rare. It causes very frequent joint infection; the cortex is absorbed instead of sequestrating. The whole of the bone is invaded and frequently leaves chronic infection in the bone marrow.

Specific antibiotic treatment, instituted as early and as radically as possible, must be the main aim of any treatment of acute hematogenous osteomyelitis in any of its 3 age forms. If started soon enough, it may control the infection before severe vascular damage has been caused in the epiphysial "anlage" and joint in the infant, in the cortex of the shaft in the child, and in the joint and bone marrow of the adult, these being the most commonly and severely affected regions in the 3 age types of bone infection. When some delay in the antibiotic treatment occurs, the main object of the treatment must be to reduce vascular damage to the utmost. Early effective radical aspiration, or preferably incisions and lavage of the affected joint in the infants and adults, and splitting of the periosteum are the most conservative procedures for the preservation of what still may remain of the blood flow in the affected bone and joint. No antibiotic will ever reach the foci of infection without the preservation of some local blood flow.

Surgical Sepsis: An Analysis of Factors Associated with Sepsis in Two Operative Procedures, 1937-1957. B. A. Barnes, G. E. Behringer, F. C. Wheelock Jr. and E. W. Wilkins Jr. New England J. Med. 261:1351-1357 (Dec. 31) 1959 [Boston].

The authors reviewed the hospital records of 9,447 selected patients who were subjected to inguinal herniorrhaphies and abdominal hysterectomies at the Massachusetts General Hospital, Boston, over a 21-year period, 1937-1957. The purpose of the study was to determine whether the currently increased incidence of sepsis in hospitals is mainly related to the patient and his complex operation or to some altered factor in the hospital environment. The incidence of a septic complication in clean abdominal herniorrhaphy and hysterectomy incision was about 4.3%. Half of these septic complications required surgical drainage or drained spontaneously. The routine use of antibiotics for "prophylaxis" against infection in clean operations studied did not alter the incidence of postoperative sepsis. Advancing age per se was not associated with more postoperative sepsis. There is no evidence for a higher proportion of staphylococcic sepsis in these operations now than in previous years.

The data show that there has been no change in the risk of sepsis in this series over the 21-year period. Consequently any increase in surgical sepsis is not the result of a change in the risk of a septic complication but rather of the altered case material requiring more elaborate surgery. Probably the older patients with their higher incidence of associated diseases and more complex surgery account for the recent increase of surgical sepsis. The authors conclude that bacteria are a necessary but not a sufficient condition for the development of a septic complication. Standardization of surgical material and treatment is essential to avoid apparent alterations in the incidence of sepsis which may masquerade as evidence for a change in the bacterial environment of the patient.

A Ten-Year Analysis of Intertrochanteric Fractures of the Femur. M. Cleveland, D. M. Bosworth, F. R. Thompson and others. J. Bone & Joint Surg. 41-A: 1399-1408 (Dec.) 1959 [Boston].

In January, 1947, at the American Academy of Orthopedic Surgeons, a report was given on 133 consecutive trochanteric fractures of the femur, treated at St. Luke's Hospital, New York. This paper is a continuation of that study, reviewing observations on 239 patients treated between January, 1947, and January, 1957. When the 1947 report was written, internal fixation of these fractures was just becoming popular. A third of the fractures in the first series were treated by traction, whereas in this second series 97.5% were treated by internal fixation. The great majority (88.7%) of the patients were women, and the average age was 75 years. The bone structure of elderly women is less resistant to trauma than is that of men of the same age.

Ten of the 239 patients with trochanteric fractures were not operated on in that 4 died shortly after admission, 5 were treated by traction, and 1, a man with hemophilia, was treated with a double-plaster spica. The remaining 229 trochanteric fractures were treated with internal fixation; all but 2 were immobilized with a one-piece Jewett nail. The average number of nail insertions was 1.54 per operation; 144 were done with one drive. The greatest number of failures occurred in fractures in which the nails were placed too high or anterior in the head of the femur (usually single drives). In the multiple-drive group, removal of the nail from a poor position and reinsertion in a good position lowered the incidence of failure of union, and carried no demonstrable adverse effects on the over-all final result. The angle of the Jewett nails varied, but in 76% the angle used was 130 degrees. The length of the nails also varied, but 90% of them were 3 to 3½ in. long. Since on the follow-up roentgenograms 10% of the nails were seen to have penetrated the articular cartilage, the authors believe that some of the nails could have been shorter. However, when the head-and-neck fragment is short, the surgeon is faced with the choice of a short nail and instability, or a long nail with later possible penetration. The authors prefer stability and possible penetration, in that a penetrating nail can later be removed, but malunion is hard to accept.

The patients were taught crutch-walking when vision, strength, balance, and general condition permitted. Twenty-one patients died before they could walk, and 49 left the hospital before they became ambulatory. Patients with nailed fractures who did walk did so, on an average, 38 days after operation. The 5 patients treated electively by traction walked, on an average, 87 days after operation—49 days later than the patients who were treated surgically. There were 24 deaths (10.5%) among the patients operated on. The causes of death in the hospital were: pulmonary emboli in 6 patients, congestive heart failure in 6, myocardial infarct in 5, pneumonia in 2, and general malnutrition and arteriosclerosis in 2; uremia, carcinomatosis, and bleeding gastric ulcer, respectively, were the causes in 3 patients. The fact that more than 60% of the patients followed up are now dead is understandable when it is considered that the average age of the patients was 75 years at the time of fracture. It was also found that there is a 16.4% chance that a patient with a trochanteric fracture will, at some time, sustain another hip fracture. This indicates a need for permanent protection.

Lytic Cocktail as Supplement in Treatment of Apparently Irreversible Shock. E. T. Madsen. Ugesk. laeger 121:1739-1743 (Nov. 5) 1959 (In Danish) [Copenhagen].

A case of apparently irreversible traumatic shock was dominated by hypoxemic damage to the brain and heart. After application of routine antishock measures, the patient's condition still seemed hopeless. Exploratory laparotomy revealed stasis in the splanchnic area. The shock subsided rapidly after injection of a "lytic cocktail," which contains drugs acting on the autonomic nervous system, and the patient recovered completely.

Severe Accidental Flaying: A Plea for Initial Conservatism. P. S. London and R. Clarke. J. Bone & Joint Surg. 41B:658-670 (Nov.) 1959 [London].

The authors report on 10 patients with severe flaying injuries of the upper and lower extremities, which were sustained in run-over accidents by 8 of the patients, and by 2 in factory accidents. About half or more of an extremity had been flayed. The results of initial conservation of undermined skin by sewing back the flaps and deferring excision until dead skin has been clearly defined proved that this is often the treatment of choice. The strongest justification for initial conservation of injured skin is that it can provide a sound covering for bone, joint, or tendon, whether damaged or not, more simply than a graft. The ease and reasonable safety of the method allow it to be used in a wide range of injuries, provided that the patient is treated within a few hours of injury after the blood lost has been made good: the separated skin appears to have some chance of survival; damaged muscle is discarded; the wound, after bleeding has been stopped, is closed with adequate technique, instruments, and suture materials; the extremity is supported by firm, even-pressure dressings and then elevated; and, in the event of discomfort, fever, swelling, or smell, a responsible surgeon is available to review the treatment. Minor infection has been common, but rarely has it affected treatment or delayed recovery to any important extent. The patients did not spend any longer time in hospital than those with wounds of comparable severity treated by immediate grafting.

NEUROLOGY & PSYCHIATRY

Intrathecal Phenol in the Treatment of Reflex Spasms and Spasticity. R. E. Kelly and P. C. Gautier-Smith. Lancet 2:1102-1110 (Dec. 19) 1959 [London].

The authors used intrathecal injections of phenol dissolved in glycerin or Myodil in the treatment of patients with reflex spasms. So far, 32 patients have been treated. All had severe spasticity of one or both legs, and 25 had disturbing and painful reflex spasms. There were 24 female and 8 male patients; the youngest treated was 2 years old, and the oldest 75. All were paraplegic except one patient with hemiplegia due to cerebral hemorrhage. The majority of the patients (20) had disseminated (multiple) sclerosis.

Solutions of phenol in Myodil or glycerin are hyperbaric, so the patient is placed on the side to be treated, in the conventional lateral lumbar-puncture position. Careful positioning is needed, with a slight downward slope of the spine. The needle is inserted between L-2 and L-3. When cerebrospinal fluid appears, the needle is advanced a further 1 mm. to prevent subdural injection; 0.5 ml. of the appropriate solution is then injected. The effects of the solutions used vary from patient to patient. The 5% glycerin solution is more effective but is liable to give rise to sensory loss and weakness. Its use should be restricted to bedridden patients in whom these complications are not so important. The Myodil solution is a perfectly safe treatment for patients who are able to walk a little, and on several occasions it has improved their gait by reducing spasticity; it is not so effective when spasms are very severe. Bladder complications have not proved a serious problem, although it is important to keep the solutions away from the lower sacral nerve roots.

Patients with paraplegia of long standing and severe contractures cannot be helped much unless they are troubled by spasms; but spasticity of lesser degree can be reduced, adding to the patient's comfort, enabling bedsores to heal, and simplifying nursing care. In some, a surprising amount of voluntary power has been unmasked by reduction of spasm.

An Evaluation of Electroencephalography in Cerebral Infarction and Ischemia Due to Arteriosclerosis. R. I. Birchfield, W. P. Wilson and A. Heyman. Neurology 9:859-870 (Dec.) 1959 [Minneapolis].

Electroencephalographic findings in 94 patients with evidence of cerebral thrombosis or infarction caused by arteriosclerosis are discussed. An attempt is made to correlate the findings with the site of the infarct, the severity of neurological abnormalities, and the duration of the lesion. Particular attention is given to the evolving changes in the electroencephalogram occurring immediately after the infarction and during the ensuing weeks and months. The usefulness of the electroencephalogram in the diagnosis and management of cerebral infarction is evaluated on the basis of these observations. In 50 of the 94 patients a neurological examination was made at the time of each encephalographic study. The electroencephalographic records in the remaining 44 patients were studied retrospectively, the patients having been examined by staff neurologists within the previous 2 years. Of the 94 patients, 73 were diagnosed as having infarction or ischemia of the cerebral hemispheres, with unilateral infarction in 48, bilateral in 18, and ischemia in 7. The remaining 21 patients had brain stem signs attributable to atherosclerosis of the vertebral-basilar artery system; 2 of these had ischemic attacks only. Illustrating case histories are presented.

The results of this study indicate the value and limitations of electroencephalography in the diagnosis of cerebral infarction. A major drawback in the practical use of electroencephalography in this disorder is the fact that only 62% of the patients with evidence of unilateral cerebral infarction had definite electroencephalographic abnormalities. It is possible that some of the patients with normal electroencephalograms actually had infarction in the brain stem, but the neurological findings did not support this diagnosis. Definite abnormalities were usually absent in patients with small, localized brain stem lesions and in patients with intermittent cerebral ischemia. Diffuse brain stem infarction or bilateral hemispheral lesions were associated with a high incidence of electroencephalographic abnormalities. Close correlation between the electroencephalographic findings and the site and severity of the neurological deficit was not observed. Serial electroencephalographic studies demonstrated a relationship between the pattern of electrical activity and the state of resolution of the pathological process in the individual patient.

Experiences with a New Iminobenzyl Derivative Antidepressive. J. de la Cruz and A. S. Martín. Med. clin. 33:122-125 (Aug.) 1959 (In Spanish) [Barcelona, Spain].

One hundred seven patients (45 males and 62 females) with psychic syndromes, which included an intense depressive component, were treated with imipramine hydrochloride (Tofranil). The most common types of depression in this group were involutional in 30 patients, reactive in 20, endogenous in 17, and arteriosclerotic in 14. Those with neurotic or reactive depression were treated as outpatients, receiving doses not higher than 500 mg. The initial dose was 50 mg. daily during 2 days, administered orally and increased gradually until the desired limit. The patients were advised to take the drug early in the afternoon in order to avoid insomnia. Those suffering from deeper depressions, sometimes of endogenous origin, received the drug by alternate routes, oral and intramuscular. Most of these patients were hospitalized, especially if they manifested suicidal tendencies. The initial doses were 50 to 75 mg. daily during 2 days, given orally, then intramuscularly, and increased gradually until 350 mg. At the end of 6 to 8 days, if there were satisfactory improvement, the maintenance phase began. The dose was gradually decreased to 50 to 100 mg., and again given by the oral route.

Thirty-one patients were cured; 40 obtained considerable improvement; 22 experienced no effects. Thirteen of the remaining 14 patients had a slight improvement, and one first showed considerable improvement, then had a relapse. The best results were obtained in patients with periodic endogenous depression, especially those in whom electroshock therapy had failed. A combined therapy with electroshock and Tofranil was effective and reduced the number of shocks. Good results were obtained in senile and arteriosclerotic depressive states. In 2 patients with paralysis agitans (Parkinson's disease) the administration of Tofranil in the dose of 50 mg. gave dramatic results. Tofranil was contraindicated in patients who had a tendency to psychomotor excitability, and it was ineffective in obsessive neurosis. Secondary effects were well tolerated and consisted of dryness of the mouth, thirst, constipation, sweating, and, at times, mild tachycardia. All these effects disappeared with interruption of the treatment. The gradual administration of the drug reduced the secondary effects to a minimum and prevented interruption of the therapy.

Tetrabenazine: New Tranquilizer with Reserpine-like Action. O. Lingjaerde. Nord. med. 62:1576-1578 (Oct. 29) 1959 (In Norwegian) [Stockholm].

Tetrabenazine was given to 25 hospitalized schizophrenic patients in daily doses which were slowly increased to a maximum of 100 mg. and then discontinued after 56 days. Sixteen patients had first been treated with reserpine; 9 had had no specific treatment for several months. In both groups more or less marked improvement occurred in about half of the patients during the treatment with tetrabenazine. Side-effects were relatively insignificant. The drug is thought to be better suited than reserpine for treatment of chronic schizophreniacs.

GYNECOLOGY & OBSTETRICS

Coagulation Studies of Patients with Abnormal Uterine Bleeding. A. J. Seaman and R. C. Benson. Am. J. Obst. & Gynec. 79:5-10 (Jan.) 1960 [St. Louis].

The possibility of an underlying hemorrhagic diathesis should be considered before performing a laparotomy, dilatation, and curettage on women with abnormal uterine bleeding. The authors report their experience with screening tests designed to identify persons with an abnormal bleeding tendency when localized bleeding is the indication for operation. The 43 women, on whom studies were made, included most of the patients with abnormal uterine bleeding seen during the past year, who had no apparent gynecologic lesions or evidence of constitutional disease.

Six of the 43 patients showed evidence of a hemorrhagic diathesis with the following findings: 1. All the patients had prolongation of the bleeding time. 2. Four patients had prolonged partial thromboplastin times, and, of these, 3 exhibited abnormal thromboplastin generation, one demonstrating a plasma factor defect and the other 2 a serum factor defect. 3. Two patients had fibrinogenopenia. 4. No abnormalities were demonstrated by the Quick time, the P and P (prothrombin and proconvertin activity), or the clot retraction test.

There was a positive family history of bleeding in 3 of the patients with hemorrhagic diathesis. Three of the 4 patients undergoing surgical procedures needed transfusions to control postoperative bleeding. Five of the 6 patients with hemorrhagic diathesis demonstrated either a positive family history and/or a personal need for transfusions to control postoperative bleeding. Three patients with hemorrhagic diathesis had normal pregnancies, delivered normal viable infants, and experienced no postpartum hemorrhage. Necessary surgical procedures should be performed only when all steps have been taken to minimize the bleeding risk. Elective operative procedures should be avoided in the patient with hemorrhagic diathesis.

Habitual Premenstrual Spotting Following Electrocauterization of the Cervix: A Newly Observed Phenomenon. L. Branscomb. Am. J. Obst. & Gynec. 79:16-23 (Jan.) 1960 [St. Louis].

A woman, who in 1943 had been treated for chronic cervicitis by electrocauterization of the cervix, returned 3 years later, stating that for the past year she had noticed a scanty brownish vaginal discharge for 7 days preceding each menstrual period. Since that time this complaint has been brought repeatedly to the author's attention. In order to discover the incidence of this type of premenstrual spotting, an attempt was made to trace 200 women who had undergone cervical cauterization from 1949 to 1951. The characteristic spotting was reported by 48 (32%) of the 153 patients who could be traced.

The premenstrual spotting develops from one month to several years after the cauterization. It occurs from 1 to 7 days preceding each menstrual period, and it may disappear spontaneously after a few months, or it may persist for many years. The bleeding comes as an ooze from small cherry-red streaks or blebs which appear on the portio of the cervix. These lesions show a characteristic microscopic picture of edema of the stroma, thinning of the overlying stratified epithelium, and extrusion of blood into the area. Eleven cases of frank cervical endometriosis and 3 of stromal endometriosis were found in this group of patients. The endometriosis could have been produced by implantation. Cauterization was done in most instances shortly after a menstrual period, but the mucosa is not intact by the onset of the next period, and there would be opportunity for implantation. In this connection it is interesting to note that Williams, in a series of 35 cases of cervical endometriosis, found that 13 had been preceded by cauterization.

Effective treatment of the postcauterization premenstrual spotting consists of surgical removal with knife or biopsy punch of the portio blebs and of the tissue about and just within the external os. The question of fundamental etiology, of cause of the rhythmic bleeding, and of the relationship of the lesion to cervical endometriosis has not been satisfactorily answered by this study. All unusual vaginal bleeding calls for meticulous investigation, but this phenomenon of premenstrual vaginal spotting after cauterization can be as easily and as definitely recognized as can ovulation bleeding.

PEDIATRICS

Influence of the Immunizing Condition of the Newborn Infant on Effectiveness of the Attenuated Poliomyelitis Vaccine. A. M. Ginty, G. Contreras and A. Ohlbaum. Rev. Chilena pediat. 30:214-222 (Sept.) 1959 (In Spanish) [Santiago, Chile].

A group of 43 newborn infants were vaccinated with attenuated poliomyelitis vaccine given orally. Vaccine with type 1 poliomyelitis virus was given during the first 72 hours of life; with type 3, at one month; and with type 2, at 2 months of age. During labor, blood had been collected from the umbilical cord for determination of the circulating passive antibodies transmitted by the placental route. Stool specimens were collected successively, and blood samples were obtained at 3 and 4 months of age. A group of 31 infants of the same age, from whom the same type of biological material was obtained, served as control.

Fifty-one stool specimens were examined soon after the administration of type 1 virus; the results were positive in 8, all viruses being identified as type 1 poliomyelitis. Of 42 specimens collected after vaccination with type 3, 16 showed positive results, with 14 strains identified as poliomyelitis viruses. After the administration of type 2 virus, 3 out of 11 specimens examined yielded viruses, with 2 of them identified as poliomyelitis. In the control group, the results were negative for poliomyelitis in the 3 examinations. There were nonpoliomyelitic viruses in 3 of 40 specimens at the second examination, and in 5 of 13 specimens at the third. In both groups the titration of the blood from the umbilical cord showed the presence of neutralizing antibodies for type 2 poliomyelitis virus in 90%, for type 1 in 88%, and for type 3 in 77% of all the infants studied. The difference between the titration of antibodies neutralizing types 2 and 3, respectively, is significant and should be interpreted as the result of a definite exposure to these 2 antigens.

The changes observed in antibody titration between the examination of blood from the umbilical cord and the blood samples taken subsequently correspond to the results of the vaccination. These changes were measured in terms of positive response (increase in antibody titration, maintenance of the titration observed at birth, or a decrease of less than 8 times) or negative response (maintenance of negative serum, i. e., absence of neutralizing antibodies, change from positive to negative serum, or a decrease of more than 8 times the preceding titration). The response was positive in 58% of the vaccinated infants and in 10% of the control group. The findings indicate that vaccination with attenuated poliomyelitis vaccine is innocuous and that its effectiveness is low, the vaccine being effective in a little more than half of the group studied. The effectiveness probably depends on the quantity of antibodies present at birth.

BOOK REVIEWS

Cancer of the Breast. Compiled and edited by Willard H. Parsons, M.D., F.A.C.S. Foreword by Warren H. Cole, M.D., F.A.C.S. Publication number 355, American Lecture Series, monograph in Bannerstone Division of American Lectures in Surgery. Edited by Michael E. DeBakey, M.D., Professor of Surgery and Chairman of Department of Surgery, Baylor University College of Medicine, Houston, and R. Glen Spurling, M.D., Clinical Professor of Surgery, University of Louisville, Louisville, Kentucky. Cloth. $7.50. Pp. 232, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1959.

This latest monograph on breast cancer is like the new maid, who, when dusting, rearranges the dust. A moratorium on such publications may be indicated. The format of the book is convenient and only minor defects in proofreading were noted. Warren Cole incorrectly applies the term "Urban operation" to the so-called "super-radical operation." Dahl-Iversen and Margottini antedate him. Should not the procedure have been described in the original way as "radical mastectomy with 'en bloc' in continuity resection of the internal mammary lymph-node chain"?

In regard to surgical reporting, it may be recalled that the Halsted-Meyer operation for breast cancer did not initiate the radical attack on mammary carcinoma. Mr. Charles Moore of Middlesex Hospital in 1867, discussing inadequate operations, stressed the necessity "in every case of removing the whole breast, unsound adjoining structures—skin, lymphatics, pectoral muscle and axillary glands." Lister in the same decade and Banks in 1882 advised similar measures. It was Halsted's full description in 1894 which supplied the real surgical impetus. Parsons reports Cole's belief that too many biopsies of the breast are being done, reliance being placed on a "well-formed clinical impression," yet in a series of 71 patients an unnecessary radical mastectomy was done in three instances.

The role of the radiologist is well outlined but the substance of the thoughts is in conflict. The author takes it for granted that "sterilization should be effected by roentgenotherapy to the ovaries"; yet he admits the impossibility of bringing about complete cessation of ovarian function by this modality. A study revealed that only 20% of the patients show a satisfactory response to ovarian radiation when an evaluation is made by the vaginal smear technique. If castration is indicated, sure, immediate, and complete withdrawal of ovarian estrogen can be accomplished only by lateral oophorectomy. The statements concerning breast cancer which develops during pregnancy or lactation are at variance with contemporary opinion.

The section on hormonal treatment would be more valuable had the author used references reported later than 1955 on this subject. The subject matter is inadequately analyzed as is the concluding chapter, where the references are wholly inadequate. The division on anatomy is too brief, and the quality of the illustrations is inferior to those of the other chapters.

The portion on surgical pathology is excellent. It is well written, clear, and concise. Not only is there an acceptable classification of breast cancer, but the section on carcinoma of mammary lobules is enlightening and fairly presents the problem of so-called "lobular carcinoma in situ." This chapter is well worth the price of the book. It might have added to the value of the book, however, if Dr. Foote had included "inflammatory breast cancer" as a part of his contribution.

Aside from the information submitted by his collaborators, the editor's contribution is more understandable as a soliloquy—the limited experience of one man. While this and his philosophy on the subject are interesting, the entire effort lacks profundity. Though it is a more recent publication than several other treatises on the same subject, it lacks the note of authority.

Arterial Embolism in the Limbs: The Clinical Problem and Its Anatomical Basis. By A. L. Jacobs, M.A., D.M., F.R.C.P., Physician to Whittington Hospital, London. Foreword by C. G. Rob, M.C., M.A., M.Chir., Professor of Surgery, University of London, London. Cloth. $8. Pp. 200, with 37 illustrations. Williams & Wilkins Company, 428 E. Preston St., Baltimore 2; E. & S. Livingstone, Ltd., 16 and 17 Teviot Pl., Edinburgh 1, Scotland, 1959.

This book carefully and concisely reports the author's 16-year experience analyzing 122 embolic episodes in 69 patients. It should prove a valuable reference for internists and surgeons interested in vascular disease. The author draws some interesting conclusions. For example, the diagnosis of embolism is rarely indicated in the presence of normal auricular rhythm except with endocarditis or infarction. One of the most common precipitating factors appears to be over-treatment of congestive failure with digitalis. In contrast, conversion of auricular fibrillation to sinus rhythm with quinidine appears to be a rare cause of embolism. Gangrene of an extremity precipitated by secondary thrombosis after embolism appears to be rare, and when secondary thrombosis occurs it is a result of stagnation in an already nonviable extremity. Persistent sensory impairment and pallor appear to be the most important prognosticating factors in determining impending gangrene.

The book is somewhat deficient from the surgical point of view as there were only six embolectomies in this analysis and these were performed mainly before the development of recent surgical techniques. The author, an internist, supports the poor results of embolectomy by reference to other authors reporting experience obtained in the 1930's, but his conclusion that there appears to be little difference between the results in medically treated and untreated persons with peripheral embolism appears justified. Anticoagulants in this experience did not seem to help the involved extremity but might be useful in preventing secondary embolism. Sympathetic nerve block did not seem to improve results. Systemic use of vasodilators was indicated as undesirable because of concomitant reduction in blood pressure. The author believes that surgical treatment by embolectomy represents the ideal form of management, particularly in the light of newly developed techniques. The work is deficient in the coverage of embolism to important visceral arteries and arteries of the cerebral circulation.

George C. Morris Jr., M.D.

Alcoholism: An Interdisciplinary Approach. Proceedings of the First Annual Conference on Community Mental Health, Social Science Institute, Washington University, 1959. Edited by David J. Pittman, Ph.D., Research Assistant, Professor, Departments of Psychiatry and Sociology, Research Associate, Social Science Institute, Washington University, St. Louis. Editorial Advisory Board: John C. Glidewell, Ph.D., and others. With foreword by John C. Glidewell, Ph.D., Program Director, Training Program in Community Mental Health Research, Social Science Institute, Washington University. Cloth. $3.75. Pp. 96. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1959.

The first section of this volume is composed of five papers from the fields of physiology, psychology, psychiatry, and sociology. Each paper deals with alcoholism as applied to one of the fields mentioned. An account of the status of research in alcoholism in each of the disciplines is described. Suggestions are made for further research. The second section of the book consists of five papers dealing with interdisciplinary communication, animal behavior, psychology, social psychiatry, and medical sociology. These are followed by a record of the discussions by the 16 contributors to the volume.

For the person experienced in the subject, this book should be of value due to its exposition of the necessity for cooperation among the disciplines dealing with alcoholism. Much of the material is necessarily repetitious as there is some overlapping in the various fields. An interesting point is the agreement that the prestige of individual disciplines is not of paramount importance, but many of the authors emphasize the importance of their own disciplines. For the novice in the field of alcoholism, the material may be less valuable. This might apply also to the clinician, but to those interested in the research aspects of the problem in the various fields explored, this book should have an appeal. For those whose interests lie in discussions of possible causes for the complex problem of alcoholism, the volume is a good one.

Marvin A. Block, M.D.

Night Vision. By Gaetan E. Jayle, professeur de clinique ophtalmologique á la Faculté de médecine de Marseille, Albert G. Ourgaud, L. F. Baisinger, M.D., and William John Holmes, M.D. Introduction by Sir Stewart Duke-Elder. [French edition published and copyrighted 1950 by Masson & Cie as *La vision nocturne et ses troubles.*] Cloth. $13.50. Pp. 408, with 181 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1959.

This highly technical book should be of interest to anyone concerned with visual physiology. The first eight chapters deal with general characteristics of night light, biochemical data on visual pigments, retinal metabolism, quantic aspect of vision, the electroretinogram, and subjective and physiological aspects of night vision. The last two chapters are devoted to the practical applications of the information contained in the first eight chapters and techniques of examination. The book is little more than a complete review of the literature. Comments by the authors on the books and articles reviewed are brief and not particularly illuminating. The bibliography is brief, many references which are cited in the text are not listed, and those which are listed are in alphabetical order and no notation is made in either the text or the bibliography indicating their connection with the text. Although this book will probably have few readers, it fills a needed place in the literature as it collates material in a rapidly changing field.

Daniel Snydacker, M.D.

The Preparation of Medical Literature. By Louise Montgomery Cross, M.A. With chapter, charts and graphs by Shirley Baty, Medical Illustrator, Memorial Center for Cancer and Allied Diseases, New York. Cloth. $10. Pp. 451, with 80 illustrations. J. B. Lippincott Company, E. Washington Sq., Philadelphia 5; 4865 Western Ave., Montreal 6; Pitman Medical Publishing Company, Ltd., 39 Parker St., London, W. C. 2, England, 1959.

Although this book is described as a handbook of a fundamental and advanced nature, it is actually an elementary approach to the subject of medical writing. It covers planning, collecting the material, writing, styling, illustrating, and editing of medical papers or books. It has illustrations and an index. One appendix contains a list of annuals and yearbooks in medical fields, and the other contains a comparative listing of journal abbreviations as used by the Current List of Medical Literature and the Quarterly Cumulative Index Medicus (both of which have now ceased publication). This book should be of some assistance to new writers, such as medical students, interns, and residents, but it offers little new material for experienced writers.

QUESTIONS AND ANSWERS

INFECTIOUS AND CONTAGIOUS DISEASE IN SMALL HOSPITALS

To THE EDITOR:—*The staff of a small general hospital with eight two-bed to three-bed units would like to know what regulations are commonly used in hospitals to isolate patients already in the hospital and those to be admitted when they have infections or contagious diseases?*

Samuel F. Nebel, M.D., Arlington, Wash.

ANSWER.—Before writing rules and regulations concerned with the handling of patients having contagious and infectious diseases, a hospital staff should survey the ability of the hospital to provide adequate means of isolation. Facilities such as single rooms with running water and toilet facilities, where strict isolation techniques can be carried out, are necessary. The average small hospital often uses the following paragraph in its bylaws: "The hospital shall admit patients suffering from all types of diseases with the exception of the acute exanthems. Patients suffering from tuberculosis or poliomyelitis may be given temporary care pending arrangements for admission to the necessary institution. Strict isolation techniques and controls will be observed." The medical and administrative staffs should make up the rules, regulations, and controls for management of patients with infections. A rigid policy should be adopted for handwashing; gowning of all attendants; the use of face masks and gloves; the use and disposal of contaminated utensils and other articles in the area such as linen; dietary facilities; and thorough cleaning of the isolation area when it is vacant. Visiting rights and receipt of mail, food, and gifts by the patients should be governed by these rules. MacEachern's book, entitled "Hospital Organization and Management" (ed. 3, Berwyn, Ill., Physicians' Record Co.), deals with methods of care of patients, methods for protection of personnel and visitors, and methods of service in the unit. Diseases such as infectious hepatitis, staphylococcic infection, lung abcesses, osteomyelitis, and others, which raise additional specific problems, all require special rules.

ORTHODONTIC TREATMENT FOR CHILDREN

To THE EDITOR:—*A 10-year-old girl has moderately severe malalignment of her teeth. Should orthodontic treatment be started immediately or should it be postponed until the teeth are more permanent and growth is almost completed?*

M.D., California.

ANSWER.—The correction and prevention of malocclusion should be started as soon as possible after diagnosis. Treatment is usually more successful and of shorter duration if it is started in early childhood, when the developmental condition of the bones permits relatively rapid realignment of the teeth, the interrelationships of the jaws are not so firmly established, and unerupted teeth can be guided into position by comparatively simple appliances and therapeutic procedures. The 10-year-old patient should be referred at once to a dentist for preliminary evaluation and to an orthodontist, if the dentist judges the condition to require such specialized treatment. The alert physician can forestall serious orthodontic and subsequent personality problems in young patients by prompt referral, when dental abnormalities are observed or suspected.

FREQUENCY OF EPILEPTIC SEIZURES IN CHILDREN

To THE EDITOR:—*Do children "outgrow" epileptic seizures, and what data may be prognostic in this regard? At what age or period of development during adolescence is it safe to begin slow discontinuation of anticonvulsant medication after the child has gone over one year without seizures? These questions are pertinent, since adolescents start to drive automobiles and become socially aware.*

M.D., Nebraska.

ANSWER.—Whether children "outgrow" epileptic attacks depends entirely on the type of seizure. Petit mal seizures are common in children, uncommon after the age of 20 years, and rare after 30 years of age. In this sense, petit mal seizures may be said to be a kind of epilepsy which may be "outgrown." This, however, refers only to petit mal which meets the following definition: minor seizures lasting less than one minute, occurring daily, and characterized clinically by short attacks of staring, short attacks of staring with some myoclonic jerks, or short akinetic seizures, when

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The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

objects held in the hands fall or are dropped, accompanied by a generalized dysrhythmia characterized by a 3-per-second wave and spike.

The slow discontinuation of anticonvulsant medication for epilepsy can start only after the patient has been seizure-free for a significant period; a simple rule of one year will not suffice. When the longest interval between seizures a patient has had is six months, one year is not a safe period. It is better to continue treatment with full doses for two to three years after the beginning of the seizure-free period, the minimum period being no less than three times the longest seizure-free interval. For example, if a patient had a previous seizure-free interval of 18 months he should continue on full medication for five years. The reduction of medication should be done slowly, with periods of three to six months between each decrease in dose.

The patient with petit mal epilepsy must be managed differently since his seizures are daily. One may begin to decrease his medication after a period of three to six months has elapsed without seizures.

PERSISTENT PELVIC PAIN

To the Editor:—*A 29-year-old woman underwent a complete oophorectomy for removal of a twisted cyst of the left ovary three years ago, and multiple follicular cysts of the right ovary were punctured during the operation. Since recovery from this operation, the patient has complained of persistent pain in the right lower quadrant of her abdomen. This pain is, at times, incapacitating and is especially severe during the first two weeks of her menstrual cycle. The right ovary is palpable and the adnexal area is tender. The cervical os is extensively eroded, but the uterus is of normal size and shape. Findings of studies of her gastrointestinal, renal, and musculoskeletal systems were normal. Hormone therapy has not been beneficial. What therapeutic management would be best for this patient? If a right oophorectomy should be necessary, should a hysterectomy be performed?*

M.D., New York.

Answer.—It is difficult to evaluate such a problem without personal examination of the given patient. This pertains particularly to removal of the remaining ovary in a young woman in whom pain and not evidence of serious organic disease is the indication, since other causes for her symptoms have apparently been excluded. If all nonsurgical treatment has failed, then removal of the ovary, together with a total abdominal hysterectomy, can be considered. This ovary gave evidence of benign cystic disease three years ago and probably still does. Hormone therapy has been tried, but no details are available. In some instances of this type, 10 mg. of norethynodrel, given orally daily for three weeks from day five of the menstrual cycle and continued for three to four cycles, has resulted in regression of the follicular cysts. Diethylstilbestrol, 5 or 10 mg., administered similarly may also be tried.

EXAMINATION OF THE EYE

To the Editor:—*Please tell me the advantages and disadvantages of use of a keratometer in measuring astigmatism. Is the retinoscope superior or inferior to the keratometer in evaluating the astigmatism of the eye? Are there any advantages to the use of cycloplegic agents other than their usefulness in examination of the eye and the relief they provide in accommodation for refraction, particularly in hyperoptic persons?*

M.D., Texas.

Answer.—The keratometer measures the astigmatism of the anterior corneal surface. It evaluates, therefore, only that part of the total astigmatism of the eye which is due to this specific surface. Retinoscopy allows an estimate of the total astigmatism of the eye, and the values thus obtained are the ones which should be considered in writing a prescription. Any one of the routine textbooks on refraction contains information on this subject. Cycloplegic agents (whose action is generally also mydriatic) have a wide therapeutic application in inflammatory conditions of the eyes, in addition to their use in the examination of the eyes.

ARTIFICIAL INSEMINATION

To the Editor:—*What investigative studies have been done on the use of frozen sperm for artificial insemination?*

Lillian Wong, M.D., San Francisco.

Answer.—Frozen semen has been used successfully in animal husbandry for many years. In human beings the method has a limited application, and no reports have appeared on the subject. If donor insemination is desired, freezing is unnecessary inasmuch as fresh semen is generally available. On the other hand, if homologous insemination is planned, the presumption is that the husband is infertile and that concentrated specimens of his semen are being accumulated for one or two well-timed inseminations. Such methods have failed, however, because the motile activity of spermatozoa from an infertile male subject is not as well preserved after freezing as is that of spermatozoa from a highly fertile male; the semen of an infertile male subject is, in most instances, qualitatively as well as quantitatively deficient. Therefore the accumulation of a large concentration of "feeble" spermatozoa serves no useful purpose.

WASHINGTON NEWS

President Opposes Compulsory Health Plans . .
Research Highlights . .
HEW Appropriations . .

PRESIDENT BACKS VOLUNTARY HEALTH PLANS

President Eisenhower restated the administration's opposition to any form of national compulsory health insurance and declared that improved medical care for the aged must be achieved through further development of voluntary insurance plans.

He made the statement at his weekly news conference, as health care of the aged came to the forefront as a political issue. Leading Democratic presidential candidates Senators John Kennedy (Mass.), Hubert Humphrey (Minn.), and Stuart Symington (Mo.) pledged their support to the principle of the controversial Forand bill that would provide federal financing of some health care for the elderly through higher social security rates.

However, the House Ways and Means Committee rejected the disputed bill by a 17-to-8 vote as it started closed-door voting on various amendments to the social security laws. The vote did not entirely rule out congressional action on the measure, however. Rep. Aime Forand (D., R. I.), sponsor of the bill, had filed a discharge petition requiring the signatures of a majority of the House in an effort to bring the legislation up for a vote by the House whatever happened in the Committee, and there was still the possibility the Senate would move on the proposal or one similar to it.

President Eisenhower said he had long been opposed to a compulsory insurance program such as that visualized in the Forand measure because it would be a definite step toward socialized medicine. A great deal of progress has been made under voluntary insurance programs, but there is still a gap for persons in low-income brackets and those in state public assistance programs for the aged, he stated.

The Department of Health, Education, and Welfare had been instructed, said the chief executive, to work out a program which would define the responsibility of the individual person and of various levels of state government.

No state at present has a health insurance program for the aged, Mr. Eisenhower noted, adding that he thought it was enough of a local problem that the states should have an interest in it.

The President said he objected strongly to placing the burden on the federal government. This poses the danger of the government meeting increased expenditures by simply printing more money, something state and local governments cannot do.

At the same time, Mr. Eisenhower said that there was strong pressure for a voluntary health insurance program to cover the problem of those not actually indigent but still with insufficient income to meet catastrophic illness costs.

Asked what the government should do in this field, Mr. Eisenhower said there are many governments—federal, state, and local—and that he objected to putting everything on the federal government.

The administration previously had notified the Ways and Means Committee that it was still studying the issue and was not prepared at that time to submit a formal recommendation for any program.

RESEARCH HIGHLIGHTS AND TRENDS

Progress during the past year on a wide range of government and government-financed medical research programs was reported by the National Institutes of Health in its annual report to Congress.

Commenting on the 1959 achievements, Surgeon General Leroy E. Burney noted, "It is difficult, if not impossible, to identify and isolate fundamental changes and broad trends in medical research as taking place in a given year.

"Looking at the recent past and considering the years ahead, we can see some of the patterns of progress," he added. "Trends in the organization of medical research and in the mobilization of its resources begin to emerge, as well as certain changes in the substance of the health sciences."

One of the major developments in the future will be the "increasing involvement of the physical sciences in the study of biological problems," Dr. Burney predicted. More attention will be given to the behavioral sciences as part of the total approach to understanding biological problems, and increased emphasis was seen on attacking environmental health hazards that promise to grow as the population rises.

"Undoubtedly science will extend and intensify its probings of the very secrets of the life processes themselves—of cells and their requirements and the events that cause their destruction or uncontrolled proliferation, of macromolecular and micromolecular particles and their action and interaction," said Dr. Burney.

In this regard, he pointed to a discovery by scientists at the National Institutes of Health and the Sloan-Kettering Institute that an isolated nucleic acid, DNA, can transform normal cells to cancer cells. "This apparently brings science one step closer

(Continued on next page)

to the hope that eventually a purposefully modified DNA may be used in the treatment of human cancer," Dr. Burney told Congress.

Some significant developments under the NIH program during the past year, although by no means all, were listed as examples of progress.

1. A primitive protein was developed from a combination of 18 amino acids, and an effort to convert proteinoids into spherules which closely resemble cells was successful. The work may be of tremendous significance in understanding how life was first formed on the earth and how primitive proteins became living cells.

2. Work significant in diagnosing kidney disorders in a study of renal aminoaciduria was reported. A scientist found a practical method, with use of paper chromatography, of analyzing amino acid concentrations in a urine sample. Patterns of the different concentrations help to indicate the presence and nature of certain diseases.

3. Noteworthy advancements were made in the studies of effects of extreme cold on animals and human beings, including the successful reanimation of mice cooled to less than 32 F and progress in determining the most effective techniques for resuscitation by means of heat and combinations of air, oxygen, and carbon dioxide.

4. Experience indicated that about one-third of patients with choriocarcinoma (a rare form of uterine cancer) who receive massive doses of the drug methotrexate experience disappearance of all signs and symptoms of cancer. This is one of the few instances in which treatment with a drug has produced complete remission in patients with advanced cancer.

5. Two derivatives of methotrexate have produced survival rates three to four times greater than achieved with methotrexate in mice with far-advanced leukemia. Some animals were believed cured.

6. Discovery of a virus producing leukemia in test animals may become an extremely valuable model test system for use in further research on the human virus-cancer problem, raising the possibility of an eventual vaccine for cancer.

7. Increasing evidence was developed that one way in which nervous tension may accelerate the development of coronary artery disease is through an elevation of the serum cholesterol level.

8. A commercially prepared vaccine was found to have provided a high degree of protection against Asian influenza among naval recruits in a special study conducted by the Navy and NIH.

9. Increasing promise was shown for research efforts on hypersensitivity as a possible cause of rheumatoid arthritis.

HOUSE GROUP APPROVES HIGHER HEW FUNDS

Federal medical research programs appeared in line for another financial boost from Congress, which has voted more funds than requested by the administration for the past six years.

The House, in the first congressional action on the health budget this year, approved 55 million dollars more than the administration asked for the National Institutes of Health medical research programs. All told, 455 million dollars was voted, compared with the 400 million requested.

The extra appropriations were approved despite assertions by Arthur S. Flemming, Secretary of Health, Education, and Welfare, that too great a federal role in medical research could harm private voluntary action by eventually usurping the field.

Of the 55-million-dollar increase, the NIH's Cancer Institute received the largest hike—$13,600,000—to a total of $102,500,000. Other large boosts were for mental health, heart, and arthritis research.

Also approved was $25,600,000 for the U. S. Public Health Service's work in combating air and water pollution and other environmental health hazards. This was $2,300,000 more than the budget. Commenting on the increase, the House Appropriations Committee said, "The unanimity of scientific opinion has added to the Committee's conviction that greater effort in controlling adverse factors in the environment is essential to the preservation of the health and well-being of the nation's population."

The HEW Department as a whole was granted 4.2 billion dollars, almost 200 million dollars more than President Eisenhower recommended. This included 45 million dollars for the program of helping localities construct sewage plants, 25 million above the request.

The measure also authorized spending of 150 million dollars for the Hill-Burton program of hospital construction next fiscal year, compared with the $126,200,000 proposed in the budget.

The bill was sent to the Senate, which in recent years has approved more money than the House for such programs.

MISCELLANY

The Senate passed and sent to the House a measure calling for the precautionary labeling of potentially hazardous substances found in households. It would require a label warning the user of any hazard in the customary use of household products and at the same time identify the dangerous ingredient for the doctor in case of an accident.

The House Appropriations Committee said that the most serious present omissions in the field of environmental health safety are in accident prevention, occupational health, and the program for milk, food, and general sanitation. An additional 1 million dollars was voted for accident prevention, "the number one cause of death for children and young adults in the prime of life."

More men should enter the nursing profession to alleviate the serious shortage of nurses, according to Leonard F. Stevens, chief nurse of the St. Cloud., Minn., Veterans Administration Hospital. "There is no reason why nursing should be limited to women," he said, pointing out that 124 of the 170 VA hospitals now have men on their staffs as professional nurses.

An official of the American Pharmaceutical Association called for federal and state legislation to restrict mail order drug houses. J. Warren Lansdowne, chairman of the APA house of delegates, made the recommendation at a meeting of the organization in Washington, D. C.

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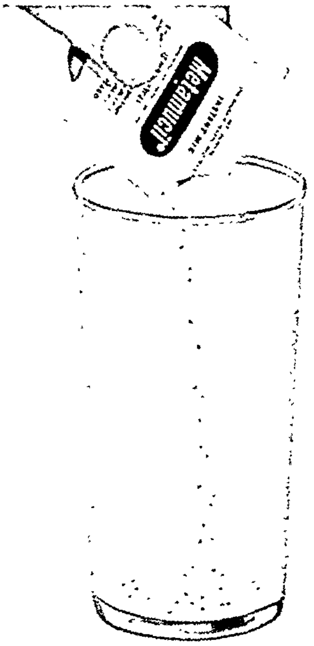

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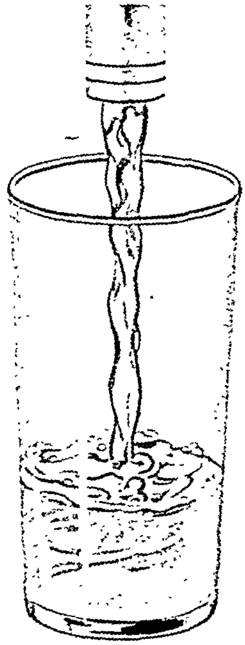

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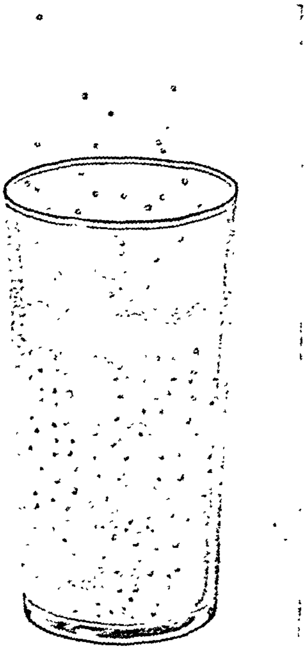

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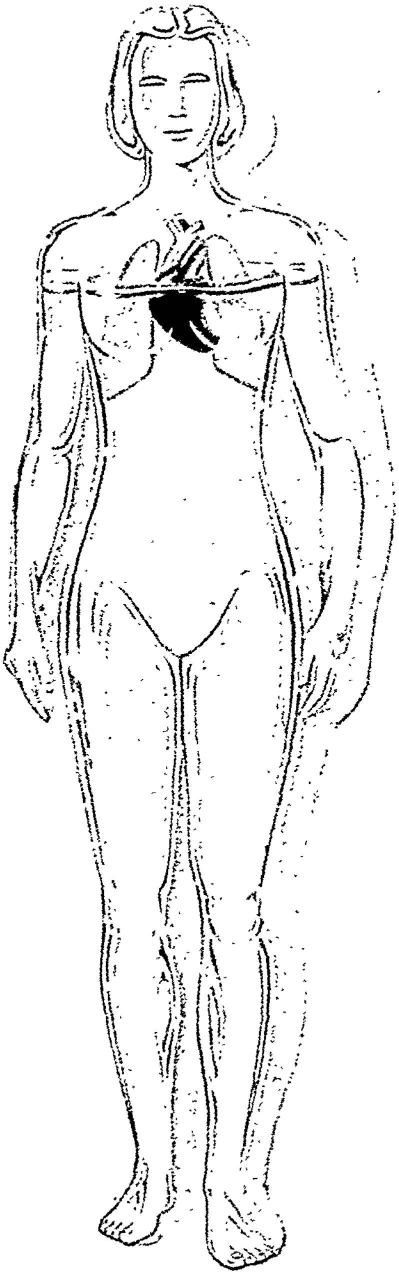

Ford, Ralph V.: Southern Med. Jl. 52: 40, (Jan.) 1959

"Hydrochlorothiazide was given to patients with edema (mild to moderate) of varied etiology..." "There were...5 women in the third trimester of pregnancy." In these patients the cumulative weight loss was 2 pounds after seven days of therapy and 4 pounds after twenty-one days. Gratifying relief of edema was observed in all patients.

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MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. F. J. L. Blasingame, 535 North Dearborn St., Chicago 10, Executive Vice-President.
1960 Annual Meeting, Miami Beach, Fla., June 13-17.
1960 Clinical Meeting, Washington, D. C., Nov. 28-Dec. 2.
1961 Annual Meeting, New York City, June 26-30.
1961 Clinical Meeting, Denver, Nov. 27-Dec. 1.
1962 Annual Meeting, Chicago, June 11-15.
1962 Clinical Meeting, Los Angeles, Nov. 25-30.

AMERICAN

1960

April

Alabama, Medical Association of the State of, Admiral Semmes Hotel, Mobile, Apr. 21-23. Mr. W. A. Dozier Jr., 19 S. Jackson St., Montgomery 4, Executive Secretary.

American Academy of Neurology, Eden Roc Hotel, Miami, Fla., Apr. 25-30. Mrs. J. C. McKinley, 4307 E. 50th St., Minneapolis 17, Executive Secretary.

American Academy of Pediatrics, Atlantic City, Chalfonte-Haddon Hall, Apr. 20-22. Dr. E. H. Christopherson, 1801 Hinman Ave., Evanston, Ill., Executive Director.

American Association for the Advancement of Science, Section on Medical Sciences, Vanderbilt University, Apr. 18-19. Dr. George R. Meneely, Vanderbilt University School of Medicine, Nashville 5, Tenn., Chairman.

American Association of Anatomists, Statler-Hilton, New York City, Apr. 11-16. Dr. Louis B. Flexner, Dept. of Anatomy, School of Medicine, Univ. of Pa., Philadelphia 4, Secretary-Treasurer.

American Association of Immunologists, Chicago, Apr. 11-15. Dr. Calderon Howe, Columbia Univ. College of Physicians and Surgeons, New York 22, Secretary-Treasurer.

American Association of Pathologists and Bacteriologists, Hotel Peabody, Memphis, Tenn., Apr. 28-30. Dr. Russell L. Holman, Dept. of Pathology, L. S. U. School of Medicine, New Orleans, La., Secretary.

American Association of Railway Surgeons, Drake Hotel, Chicago, Apr. 7-9. Mr. *Chester C. Guy, 5800 Stony Island* Ave., Chicago 37, Executive Secretary.

American College Health Association, Toronto, Canada, Apr. 27-30. Dr. Norman S. Moore, Cornell University, Gannett Clinic, Ithaca, N. Y., Secretary Treasurer.

American College of Physicians, Mark Hopkins & Fairmont, San Francisco, Apr. 4-9. Dr. Edward C. Rosenow Jr., 4200 Pine St., Philadelphia 4, Executive Director.

American College of Sports Medicine, Saxony Hotel, Miami Beach, Fla., Apr. 22-24. Grover W. Mueller, M.S., Parkway at 21st St., Philadelphia 3, Secretary.

American College of Surgeons, Sectional Meeting, Hotel Leamington, Minneapolis, Apr. 11-13. For information write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American College of Surgeons, Sectional Meeting, Kahler Hotel, Rochester, Minn., Apr. 14. For information write: Dr. H. P. Saunders, 40 E. Erie St., Chicago 11.

American Dermatological Association, Inc., Boca Raton Hotel, Boca Raton, Fla., Apr. 8-12. Dr. Wiley M. Sams, 308 Ingraham Bldg., Miami 32, Fla., *Secretary.*

American Physiological Society, Chicago, Apr. 11-15. Ray G. Daggs, D.Sc., 9650 Wisconsin Ave., Washington 14, D. C., Executive Secretary.

American Proctologic Society, Shamrock Hilton Hotel, Houston, Texas, Apr. 25-27. Dr. Norman D. Nigro, 10 Peterboro, Detroit 1, Secretary.

American Public Health Association, Southern Branch, Memphis, Tenn., Apr. 13-15. Dr. L. M. Graves, Shelby County Health Department, Memphis, Tenn., Chairman, Local Arrangements Committee.

American Society for Artificial Internal Organs, Pick-Congress Hotel, Chicago, Apr. 10-11. Dr. Charles K. Kirby, 3400 Spruce St., Philadelphia 4.

American Society of Biological Chemists, Inc., Chicago, Apr. 11-16. Dr. Frank W. Putnam, Dept. of Biochemistry, Univ. of Florida, Gainesville, Secretary.

American Society for Experimental Pathology, Pick-Congress Hotel, Chicago, Apr. 11-15. Dr. J. F. A. McManus, Univ. of Alabama Med. Center, Birmingham, Ala., Executive Secretary.

American Society for Pharmacology and Experimental Therapeutics, Inc., Chicago, Apr. 10-16. Dr. Karl H. Beyer Jr., Merck Sharp and Dohme Research Labs., West Point, *Pa., Secretary.*

Andrew, John A., Clinical *Society*, Tuskegee Institute, Alabama, Apr. 24-29. *Dr. Eugene H. Dibble, Memorial* Hospital, Tuskegee Institute, Ala., Secretary.

Arkansas Medical Society, Pine Bluff, Apr. 18-20. Mr. Paul C. Schaefer, 218 Kelley Bldg., Fort Smith, Ark., Executive Secretary.

Connecticut State Medical Society, *Hamden* High School, Hamden, Apr. 26-28. Dr. William R. Richards, 160 St. Ronan St., New Haven, Conn., Secretary.

Florida Medical Association, Robert Meyer Hotel, Jacksonville, Apr. 8-12. Mr. W. Harold Parham, 735 Riverside Ave., Jacksonville 3, Fla., Executive Director.

Harvey Cushing Society, Fairmont Hotel, San Francisco, Apr. 13-17. Dr. Edmond J. Morrisey, 450 Sutter St., San Francisco, Chairman.

Industrial Medical Association, *Rochester*, N. Y., Apr. 26-29. Mr. Clark D. Bridges, 28 E. Jackson Blvd., Chicago 4, Managing Director.

Iowa State Medical Society, Savery Hotel, Des Moines, Apr. 24-27. Mr. Donald L. Taylor, 529 36th St., Des Moines 12, Iowa, Executive Director.

Maryland, Medical and Chirurgical Faculty of the State of, The Alcazar, Baltimore, Apr. 20-22. Mr. John Sargeant, 1211 Cathedral St., Baltimore 1, Executive Secretary.

Mid-Central States Orthopaedic Society, Wichita, Kan., Apr. 8-9. *Dr. H. O.* Marsh, 3244 E. Douglas, Wichita 8, Kan., Secretary.

Nebraska State Medical Association, Hotel Cornhusker, Lincoln, April 25-28. Mr. M. C. Smith, 1315 Sharp Building, Lincoln 8, Neb., Executive Secretary.

North Dakota State Medical Association, *Dacotah* Hotel, Grand Forks, Apr. 30-May 3. Mr. Lyle A. Limond, Box 1198, Bismarck, N. D., Executive Secretary.

North Pacific Society of Neurology and *Psychiatry*, Benjamin Franklin Hotel, Seattle, Washington, Apr. 8-9. Dr. Thomas H. Holmes, University of Washington, Seattle 5, Secretary-Treasurer.

Society of Head and Neck Surgeons, *Sheraton* Hotel, Philadelphia, Apr. 18-19. Dr. Harry W. *Southwick*, 30 N. Michigan Ave., Chicago 2, Secretary-Treasurer.

Society of Neurological Surgeons, Olympic Hotel, Seattle, April 18-19. Dr. Guy L. Odom, Duke University Center, Durham, N. C., Secretary.

Southeastern *Dermatological* Association, Nashville, Tenn., Apr. 30-May 1. *Dr. Robert N. Buchanan Jr., 706 Church St.*, Nashville, Tenn., Organizing Physician.

Tennessee State Medical Association, The Maxwell House, Nashville, Apr. 10-13. Mr. Jack E. Ballentine, 112 Louise Ave., Nashville 5, Tenn., Executive *Director.*

Texas Medical Association, Hotel Texas, *Fort Worth*, Apr. 9-12. Mr. C. Lincoln Williston, 1801 *N. Lamar Blvd., Austin, Texas*, Executive Secretary.

May

Academy of Psychoanalysis, Hotel Claridge, Atlantic City, N. J., May 7-8. Dr. Joseph H. Merin, 125 E. 65th St., New York 21, Secretary.

Aerospace Medical Association, Americana Hotel, Bal Harbour, Fla., May 9-11. Dr. William J. Kennard, Aerospace Medical Association, Washington Natl. Airport, Washington 1, D. C., Secretary-Treasurer.

American Association for Cleft Palate Rehabilitation, Brown Palace Hotel, Denver, May 12-14. D. C. Spriestersbach, Ph.D., University Hospitals, Iowa City, Iowa, Secretary-Treasurer.

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American Association on Mental Deficiency, Lord Baltimore Hotel *Baltimore*, May 16-21. Mr. *Neil A. Dayton*, P. O. Box 51, Mansfiel Depot, Conn., Executive Secretary-Treasurer.

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American Association for Thoracic Surgery, *Deauville Hotel*, Miam Beach, Fla., May 11-13. Dr. Hiram T. Langston, 7730 Carondelet Ave St. Louis 5, Secretary.

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American Federation for Clinical Research, Chalfonte-Haddon Hal Atlantic City, N. J., May 1. Mr. James E. Bryan, 250 W. 57th St., Ne York 19, Executive Secretary.

American Gynecological Society, Williamsburg Inn, Williamsburg, Va May 30-June 1. Dr. Andrew A. *Marchetti*, Georgetown Univ. Hos Washington 7, D. C., Secretary.

American Ophthalmological Society, The Broadmoor, Colora Springs, Colo., May 16-18. Dr. Maynard C. Wheeler, 30 W. 59th S New York 19, *Secretary.*

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Association of American Physicians, Haddon Hall, Atlantic City, N. May 3-4. Dr. Paul B. Beeson, Yale Univ. *School of Medicine*, N Haven 11, Conn., Secretary.

Association of Surgeons of the Southern Railway System, Charl ton, S. C., May 9-10. Dr. Rudolph M. Landry, 707 Walnut St., Chat nooga 2, Tenn., Program Chairman.

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Hawaii Medical Association, Honolulu, May 12-15. Mr. Lee McCasl 510 S. Beretania St., Room 200, Honolulu 13, Hawaii.

Illinois State *Medical* Society, Hotel Sherman, Chicago, *May 24-* Dr. George F. Lull, 185 N. Wabash, Chicago, Secretary.

Kansas Medical Society, Baker Hotel, *Hutchinson, May* 2-5. Mr. Oli E. Ebel, 315 W. Fourth, Topeka, Kan., Executive Secretary.

Louisiana State Medical Society, Capitol House, Baton Rouge, M 2-4. Dr. C. Grenes Cole, 1430 Tulane Ave., New Orleans 12, *Secreta* Treasurer.

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TRACHOMA–STUDIES OF ETIOLOGY, LABORATORY DIAGNOSIS, AND PREVENTION

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and
Paul B. Johnston, Ph.D., Taipei, Taiwan (Formosa)

Material from 116 human eyes infected with trachoma was used successfully for the isolation of viruses by culturing in the yolk sac of chick embryos. Five strains of virus were isolated. All five killed embryos on second passage, and all five fixed complement with both serum from patients with lymphogranuloma venereum and a guinea pig psittacosis antiserum. The virus thus made available for laboratory study was used in tests for sensitivity to drugs. Penicillin, sulfisoxazole, and oxytetracycline were effective against the virus even in the smallest amounts used. The virus produced typical acute follicular conjunctivitis in six human volunteers. A vaccine was produced from the virus and elicited a significant antibody response in monkeys and human subjects. Evidence that the vaccine had both preventive and curative value was obtained.

FOUR hundred million people are afflicted with trachoma, one of the oldest, most widespread diseases and the world's leading cause of blindness. Until recently, trachoma remained one of the few virus diseases in which the causative organism was not available for study. In 1957 T'ang and his associates in Peiping reported the isolation of three strains of virus from trachomatous eyes in the yolk sac of emybryonated eggs.[1] These isolations were confirmed at the Lister Institute in London.[2] The English workers isolated additional strains from persons with trachoma in Gambia, Africa, and produced an eye infection in a human volunteer with one of their strains. The main innovation of the Chinese workers was the use of streptomycin to control bacterial contamination in the egg culture of eye specimens. Subsequently, reports have appeared of virus isolations in the yolk sac of chick emybryos from patients with trachoma in Saudi Arabia,[3] Israel,[4] and Taiwan (Formosa).[5] Thus, within two years, the formerly elusive trachoma virus has been isolated in several laboratories. The availability of the virus provides a greatly improved opportunity for profitable research on trachoma.

Studies of trachoma have been underway at the Naval Medical Research Unit no. 2 (NAMRU-2) for one year. The results will be reported under

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From the United States Naval Medical Research Unit no. 2 (NAMRU-2), the Department of Ophthalmology, National Taiwan University College of Medicine, and the Department of Medicine, University of Chicago.
Read before the 52nd annual meeting of the Formosan Medical Association, Taipei, Nov. 21, 1959.

the following headings: (1) virus isolation, (2) human volunteer infections, (3) host range of trachoma virus, (4) antibiotic sensitivity of trachoma virus. (5) serology, (6) skin test, and (7) trachoma vaccine.

Virus Isolation

A total of 150 eye specimens obtained on Taiwan have been cultured in the yolk sac of developing chick embryos. Most of the specimens were obtained from first-grade school children. The rest came from aborigines, both adults and children. Details of specimen collection and culture in embryonated eggs are presented in a separate report.[5] Briefly, specimens were collected with dry cotton-tipped applicator sticks, placed in brain-heart infusion broth, and frozen at −65 C. The yolk sacs of five 6-to-8-day-old embryonated eggs were inoculated with 0.2 ml. of each specimen, to which streptomycin had been added in an amount so that each egg received 4 mg. The clinical diagnosis of trachoma was based on the modified MacCallan classification,[6] by which stage 1 is trachoma at onset, stage 2 is established trachoma, stage 3 is cicatrizing trachoma, and stage 4 is cicatrized or healed trachoma.

TABLE 1.–*Isolation of Trachoma Virus in Yolk Sac of Chick Embryo from Eye Specimens Collected on Taiwan*

Eye Condition	Specimens Cultured, No.	Viruses Isolated, No.
Trachoma		
Doubtful	17	0
Stage 1	11	0
Stage 2	34	4
Stage 3	25	1
Chronic follicular conjunctivitis	24	0
Normal-appearing	5	0
Total	116	5

Table 1 gives the results of the culture of 116 eye specimens. The cultures of 34 eye specimens were not completed because of bacterial contamination. Five strains of virus were isolated. Four of them (TW 10, 21, 89, and 97) were from 34 persons with stage-2 trachoma and one (TW 29) was from 25 persons with stage-3 trachoma. The four persons with stage-2 trachoma from whom virus was isolated were 6-to-7-year-old school children, while the one with stage-3 trachoma was an adult male aborigine. With the same isolation techniques, no viruses were isolated from 17 persons with doubtful trachoma, 11 with stage-1 trachoma, 24 with chronic follicular conjunctivitis, and 5 with normal-appearing eyes.

Elementary bodies were seen on first passage of three of the strains isolated and on second passage of the other two. All five strains killed embryos on second passage. Three of the strains have been through from 16 to 19 egg yolk sac passes. Elementary bodies resembling those of the psittacosis–lymphogranuloma venereum group are regularly seen in yolk sac smears of the five Taiwan trachoma strains. Each strain was tested as antigen in the complement fixation (CF) test with serum from a patient with lymphogranuloma venereum and with a guinea pig psittacosis antiserum. All five strains fixed complement with both serums, thus demonstrating a serologic relationship of the trachoma viruses to the psittacosis–lymphogranuloma venereum group.

Human Volunteer Infections

The World Health Organization's Expert Committee on Trachoma[7] has insisted that the final proof that a virus under cultivation is the cause of trachoma should be the production of typical trachoma in human volunteers after sufficient passages in culture to eliminate by dilution any virus of the original inoculum. In order to fulfill this requirement, seven blind volunteers without evidence of trachoma infection were recruited from the Taipei Blind and Deaf School. The experiment was designed so that the examining ophthalmologist

TABLE 2.–*Summary of Results of Human*

Volunteer No.	Sex	Age, Yr.	Eye	Inoculum*	1	2	3	4	5	6
1.	M	11	Left	Tr^{-1}	+ (−)	++ V	++ V	+ ...	++ V	++ V
2.	M	17	Right	Tr^{-1}	++ (−)	+ V	+ V	+ ...	+ V	++ V
3.	M	21	Right	Tr^{-1}	+ (−)	+ ...	+ V	++ ...	+ V	+ V
4.	M	12	Left	Tr^{-2}	+ (−)	+ ...	+ V	+ ...	+ V	++ V
			Right					Tr^{-4}‡	+ V	+ ...
5.	M	22	Left	NYS	0 (−)	0 (−)	0 (−)	... Tr^{-2}	+ V	+ ...
6.	F	22	Left	NYS	0 (−)	0 (−)	0 (−)			
7.	F	18	Left	Av4	0 (X)	0 (X)	0 (−)			
			Right					Tr^{-3}	+ V	+++ ...

* Tr^{-1} to Tr^{-4} refers to 10^{-1} to 10^{-4} dilution of yolk sac TW10 trachoma strain; NYS = normal yolk sac; and Av4 = adenovirus type 4.

† + to +++ arbitrary gradation of number of inclusion bodies seen on conjunctival smear; o = negative smear. V = reisolation of trachoma

‡ Second inoculation August, 1959.

was not aware of what material had been given to the volunteers or of the results of laboratory studies performed as the experiment progressed.

Some of the results of this experiment are summarized in table 2. The first series of inoculations was carried out in July, 1959. At that time four volunteers were inoculated in one eye with either 10^{-1} or 10^{-2} dilution of yolk sac TW10 trachoma strain in the seventh egg passage with an egg ID_{50} of 3.6 and LD_{50} of 1.8. Two volunteers were inoculated with normal yolk sac, and one was inoculated with adenovirus type 4. Within two or four days an acute follicular conjunctivitis had developed in five of the volunteers. The two receiving normal yolk sac material showed no evidence of infection. For about two weeks the clinical picture of the five infected volunteers was indistinguishable. However, by the end of the second week, it was apparent that the infection in the patient with adenovirus type 4 was less severe than in the others. In the adenovirus infection, there was not as much congestion or edema and fewer follicles appeared and they were more transparent. After two weeks the intensity of the conjunctivitis began to decrease and by one month after inoculation the eye appeared normal. No pharyngitis occurred in association with this infection. Adenovirus type 4 was reisolated from the inoculated eye during each of the first two weeks.

The gross appearance of the follicular conjunctivitis associated with trachoma virus infection showed progression in intensity for two months, and then the acute signs began to slowly improve. Six days after inoculation, typical inclusion bodies were demonstrated in the conjunctival cell smears of the volunteers infected with trachoma virus. No inclusion bodies were seen in the other three volunteers. An estimate of the number of inclusion bodies present on the conjunctival cell smears at weekly intervals during 19 weeks of observation can be seen in table 2. In general, there was an increase in the number of inclusion bodies demonstrated during the first two months after infection, with a tendency toward decrease in their numbers subsequently. The number of inclusions on smear roughly paralleled the clinical impression of intensity of conjunctivitis. Trachoma virus was reisolated from two of the four trachoma infections in two weeks, from all four during the third week after inoculation, and subsequently several times for a total of four to six reisolations from each infected eye.

Volunteer Infections with Trachoma Virus

Weeks After First Inoculation†												
7	8	9	10	11	12	13	14	15	16	17	18	19
+++ ...	+++ V	+++ ...	++ ...	++ ...	+ ...	++ ...	+ ...	+ V	++ ...	+ ...	++ ...	± ...
++ ...	+ V	++ ...	+ ...	++ ...	+ V	+++ ...	+ ...	++ ...	+ ...	+ ...	++ ...	+ ...
+ ...	++ V	+ ...	+ V	0 ...	+ ...	+ ...	+ ...	+ V	0 ...	+ ...	± ...	+ ...
+++ ...	+++ V	++ ...	++ ...	++ ...	++ ...	++ ...	+ ...	+ V	0 ...	+ ...	+ ...	+ ...
+ (—)	+ ...	++ ...	+ ...	++ ...	+ V	... ...	+ ...	+ (—)	+ ...	+ ...	++ ...	+ ...
+ ...	++ ...	+ ...	+ ...	+ ...	+ (—)	++ ...	+ ...	+ (—)	++ ...	+ ...	+ ...	0 ...
	+++ ...	+++ V	+++ ...	+++ ...	+++ ...	+++ ...	+ ...	+++ V	++ ...	++ ...	+++ ...	+++ ...
+++ ...	++ V	+++ ...	+++ ...	+++ ...	+++ ...	++ ...	++ ...	+++ V	+ ...	+++ ...	++ ...	+++ ...

virus in egg yolk sac; (—) = negative isolation attempt. First inoculation July 17, 1959. X = adenovirus type 4 isolated.

At the end of one month's observation, one of the control subjects was dismissed from the study. The other two were infected with higher dilutions of trachoma virus and at the same time the uninvolved eye of one of the volunteers originally given trachoma virus was also inoculated. Within six days after infection with 10^{-2} to 10^{-4} dilutions of TW 10, inclusion bodies were seen on conjunctival scrapings and trachoma virus was reisolated in the yolk sac of chick eggs from all three eyes. The rapid reisolation of the virus from this second group of infections was probably due to more thorough swabbing while obtaining specimens. The intensity and the course of the second group of trachoma infections has been similar to the first. A spread of infection to the uninoculated eye occurred in volunteer 7 within one month after he was infected, with the occurrence of an acute follicular conjunctivitis. Typical inclusion bodies of trachoma and virus reisolation were obtained from the uninoculated eye.

The clinical illness in the six volunteers was more acute than in a patient with natural trachoma. For example, periauricular lymphadenopathy persisted in all volunteers, and in addition there has been more conjunctival petechial hemorrhage and conjunctival pseudomembrane than would be expected in patients with early natural trachoma. Bulbar conjunctival follicles appeared in all of the volunteers.

Despite the acute nature of the disease, the volunteers remained comfortable throughout the experiment.

With the exception of volunteer 1, the cornea of the infected eyes of the volunteers had been so damaged prior to the experiment that it was not possible to state whether or not pannus developed in response to the experimental infection. Corneal disease due to the trachoma virus was proved in volunteer 2 by the demonstration of typical inclusion bodies in corneal cell smears. In volunteer 1, initial pannus and epithelial keratitis on the upper part of the cornea were first seen during the fourth week after inoculation. Vascularization continued into transparent corneal tissue. The pannus formation progressed for three months and has been stationary subsequently. The maximum extent of infiltration and vascularization has been 1 mm. The epithelial keratitis disappeared during the fourth month. Dr. S. Maffei, World Health Organization consultant ophthalmologist to Taiwan, confirmed these clinical diagnostic findings of trachoma.

The serologic response to infection in these volunteers will be presented in the section on serology, and the effect of trachoma vaccine on three of the volunteers will be discussed in the section on vaccine.

Host Range of Trachoma Virus

Various members of the psittacosis–lymphogranuloma venereum group of viruses infect different tissue of a variety of laboratory animals. So far, the monkey eye is the only tissue of any laboratory animal that has been infected with the Taiwan trachoma viruses. The following animals and birds have been inoculated with one of the Taiwan strains, usually by several routes, without any resulting evidence of infection: adult mice, infant mice, mice after radiation with 400 r, guinea pigs, white rats, golden hamsters, rabbits, monkeys (except intraocularly), parakeets, and lonchuras. Attempts to grow trachoma virus in series on the amniotic or allantoic membrane of the chick egg have failed. Extensive efforts to grow trachoma virus in HeLa cell, monkey kidney, and chicken embryo tissue cultures with a variety of mediums have been unsuccessful.

The trachoma virus has been shown to possess a toxin similar to the other members of the psittacosis-lymphogranuloma venereum group by its ability to kill mice within 24 hours after intravenous inoculation.[8] Strains TW 10, 21, and 29 have killed mice when 10 to 20% yolk sac suspensions were inoculated intravenously.

The Taiwan monkey, Macaca cyclopis, develops an acute follicular conjunctivitis when inoculated in the eye with strains TW 10 and 29. The onset of conjunctivitis was seen 4 to 11 days after inoculation and persisted for two to three months. Although only questionable atypical inclusions have been found in monkey conjunctival cell smears, the trachoma virus has been reisolated from infected monkey eyes, on several occasions, more than two weeks after inoculation. The infection caused by trachoma virus in monkeys is self-limited, exhibits no corneal lesions, and does not progress to scar formation. The monkey infection due to the yolk sac virus appears to be similar to that which has been described in monkeys after inoculation of eye scrapings from trachoma patients.[9]

Table 3.–*Effect of Antibiotics and Sulfonamide on Growth of TW29 Trachoma Virus in Embryonated Eggs**

Drug	Amount per Egg	Day of Death of Embryo and Number of Elementary Bodies in Yolk Sac Smear†					
Control		5+	5+	6+++	7+	7+	8+
		5+	6++	7+	7+	7++	8++
Streptomycin	0.5 mg.	6++	6++	7+	7+	7+	7+++
Penicillin	10 units	7	—	—+	—+	...	...
	200 units	—	—	—	—	—	—
Sulfisoxazole	2 mg.	—	—	—	—	—	—
	10 mg.	10	—	—	—	—	—
Chloramphenicol	0.2 mg.	9+	10++	12++	12++	13+++	—++
	1.0 mg.	12	—	—	—+	—+	—+
Oxytetracycline	0.1 mg.	9	—	—	—	—	
	0.5 mg.	—	—	—	—	—	—
Furaltadone	0.1 mg.	11++	12++	13++	—+	—+	...
	0.5 mg.	—	—	—	—	—	—

* 10% yolk sac suspension of virus and antibiotic or sulfonamide mixed and immediately inoculated into yolk sac of 7-day-old embryo.

† All embryos not dying (—) were opened on 13th day and yolk sac smear examined. + to +++: number of elementary bodies seen on smear.

Antibiotic Sensitivity of Trachoma Virus

There is no general agreement on the most effective chemotherapy for natural trachoma. With the availability of the trachoma virus for study in the laboratory, determination of the sensitivity of the virus to antimicrobial drugs became possible. Table 3 presents the results of tests performed with the TW 29 trachoma virus and a series of antibiotics, a sulfonamide, and a nitrofurazone compound in the egg yolk sac. Streptomycin, 0.5 ml. per egg, had no effect against the virus. The control eggs and those given streptomycin died between five and eight days after inoculation. The other drugs tested, penicillin, sulfisoxazole, chloramphenicol (Chloromycetin), oxytetracycline (Terramycin), and furaltadone (Altafur) all showed activity against the virus by preventing death of the embryos and reducing or eliminating evidence of infection as represented by the presence of elementary bodies in yolk sac smears. Two-tenths of one milliliter of chloramphenicol and 0.1 ml. of furaltadone per egg were only partially effective against the virus. All other drugs tested were highly effective even in the smallest amounts used. The results reported in table 3 have been repeated with another trachoma strain. T'ang and co-workers[1] have reported their trachoma viruses to be sensitive to penicillin, sulfonamides, and oxytetracycline.

Serology

In the past there have been several attempts to demonstrate complement fixing antibodies in trachoma patients with use of psittacosis or lymphogranuloma venereum antigens.[9] The results have been irregular and the method has not been used for diagnosis. Phenolization and heating have been shown to produce improved complement fixing antigens with members of the psittacosis–lymphogranuloma venereum group.[10] The antigens produced are group-specific rather than strain-specific. CF tests in this laboratory with trachoma virus antigen prepared with phenol and heat failed to demonstrate antibodies in a series of persons with natural trachoma. When an antigen prepared from yolk sac suspensions by purification procedures was used, complement fixing antibodies could be measured in trachoma patients. This antigen has also been used as a vaccine. Details of the purification studies will be presented in a separate report.[11] In short, the "purified" trachoma virus antigen was prepared as follows. Yolk sac suspensions were digested with trypsin and then subjected to several alternate high-speed and low-speed centrifugation cycles to free the elementary bodies from the yolk sac material. The elementary bodies were further purified by precipitation with polymyxin, followed by elution in cold buffered saline. They were inactivated with formalin. Examples of the results with purified preparations used as complement fixing antigens with serums from humans infected with trachoma, lymphogranuloma venereum, and psittacosis are shown in table 4.

TABLE 4.—*Specificity of Trachoma Antigens Prepared by Purification in Complement Fixation Test with Human Serum*

	Serum Antibody Titer† Antigens				
Patient Serum*	LGV Group	Psittacosis (6 BC) Group	TW10 Group	TW10 Partially Purified	TW10 "Purified"
LGV	128	64	32	0	0
LGV	256	256	64	8	0
Psittacosis	64	64	64	16	0
Psittacosis	32	64	32	8	0
Trachoma	0	0	8	32	64
Trachoma	0	0	0	8	32

* The LGV (lymphogranuloma venereum) and trachoma serums were from patients with active disease. The psittacosis serums were from patients convalescent from pneumonitis, kindly supplied by Dr. Helen L. Casey, Chamblee, Ga.

† All CF antibody titers are reciprocals of the highest original serum dilution with a +++ end-point. 0 <8. The group antigens were prepared from yolk sac suspensions with phenol and heat.[10] The partially purified antigen was digested with trypsin and purified by 3 cycles of high speed centrifugation. The "purified" antigen was in addition precipitated with polymyxin.

Results with group antigens made from these three organisms are presented for comparison. The group antigens reacted in high titer with the serums from patients with lymphogranuloma venereum and psittacosis and in low titer or not at all with serums from patients with trachoma. The partially purified trachoma antigen reacted best with trachoma serum and poorest with lymphogranuloma venereum serum. The antigen after precipitation with polymyxin produced the highest antibody titers in trachoma serums and failed to react at all with the other serums. Lymphogranuloma venereum and psittacosis are closely related; trachoma seems to be more distantly related to the group and to be somewhat closer to psittacosis than to lymphogranuloma venereum. The "purified" trachoma antigen appears to measure specifically trachoma antibodies.

TABLE 5.—*Complement Fixation Antibody Titers in Serums of First-Grade School Children on Taiwan in Relation to Condition of Their Eyes, with Use of Purified Trachoma Virus Antigen*

		Complement Fixation Titer*						
Diagnosis	No. Tested	0	4	8	16	32	64	% Positive
Trachoma								
Doubtful	26	19	...	5	2	...	...	27
Stage 1	21	15	1	3	2	...	...	29
Stage 2	187	115	17	36	14	2	4	39
Stage 3	82	63	7	3	9	...	...	23
Stage 4	4	3	1	...	...	...	...	25
Chronic follicular conjunctivitis	117	88	7	13	8	1	...	25
Folliculosis	11	11	...	...	...	...	...	0
Normal-appearing	57	56	...	1	...	...	...	2
Total	505	370	33	61	35	3	3	

*Antigen is strain TW-29. Titer is expressed as reciprocal of original serum dilution with +++ end-point. 0=<4.

The results of testing 505 serums of first-grade school children on Taiwan in the CF test with "purified" trachoma antigen are shown in table 5. These results are presented in relation to the clinical diagnosis of the eye condition. All children were from areas in which mild trachoma is endemic. Here and elsewhere in this paper complement fixation antibody titers will be presented as the reciprocal of the greatest original serum dilution giving at least three-fourths (+++) fixation. Thirty-nine per cent of the serums of 148 children with stage-2 trachoma showed a titer of four or greater in the CF test. The greatest number of reactions were at a serum titer of 8, with some reacting at 16, 32, and 64. From 23 to 29% of serums from children with the following diagnosis reacted in the CF test: doubtful trachoma; trachoma stages 1, 3, and 4; and chronic follicular conjunctivitis. One child of 57 with supposedly normal eyes tested showed trachoma antibodies. None of 11 serums from children with folliculosis showed antibodies. Since the test is believed to be specific for trachoma, these findings raise the question of the accuracy of diagnosis of nontrachomatous chronic follicular conjunctivitis, which in 1958 was made on 16% of the first-grade school children on Taiwan. The World Health Organization's consultant ophthalmologist on Taiwan has stated that in his opinion a portion of the children usually diagnosed as having chronic follicular conjunctivitis had trachoma infections of the "nonevolutive" (nonprogressive) type.[12] This clinical impression is supported by the serologic results.

In addition to the 505 children with mild trachoma, two small groups with more severe trachoma have been tested with the "purified" complement fixing antigen. Serums were available from 34 persons of all ages and at all stages of the disease, who resided in two areas of Taiwan in which moderately severe trachoma is endemic. Of these serums 21, or 62%, reacted in the CF test. In addition, nine serums from Egyptian children in Cairo, aged 5 to 15 years, with trachoma stages 2 to 4, were supplied by Dr. Abdelfaltah M. Mohamed. Eight of these nine serums reacted, seven having antibody titers of 16 to 64.

Table 6.—*Complement Fixation Antibody Response in Human Volunteers to Experimental Trachoma Infection*

			Serum Antibody Titer, Days After Infection with TW10*											
Volunteer No.	Age, Yr.	Sex	0	12	23	38	52	68	80	95	109	116	122	143
1	11	M	0	0	...	0	0	0	8	8	16	...	16	16
2	17	M	0	16	...	8	16	16	16	16	32	...	16	16
3	21	M	4	4	...	32	32	(32)	(64)	(64)	(64)	...	(64)	(64)
4	12	M	0	0	...	0	0	(8)	(16)	(16)	(16)	...	(16)	(32)
5	22	M	0	0	8	(32)	(32)	(32)	(32)	(64)	...	(32)	...	...
7	18	F	0	0	16	8	8	8	16	32	...	8	...	...

* Those results given in parentheses were influenced by trachoma vaccine given at monthly intervals beginning 53 days after infection of volunteers 3 and 4 and 25 days after infection of volunteer 5. 0=<4

CF antibodies with the "purified" trachoma antigen have been demonstrated in the human volunteers infected with TW10 strain. The antibody titer of these volunteers with acute trachoma at various intervals after inoculation during 143 days of observation is shown in table 6. The time interval when antibodies could first be demonstrated varied considerably among the volunteers. Volunteer 2 had a titer of 16 by 12 days after infection and volunteers 5 and 7 had antibodies after 23 days. Volunteer 3 had a titer of 4, a level of questionable significance, prior to infection, which rose to 32 after 38 days. Volunteer 1 finally showed a titer of 8, 80 days after infection and about 50 days after the appearance of initial pannus. Volunteer 4 never did have circulating antibody until two weeks after receiving trachoma vaccine, which was 68 days after infection in the left eye and 38 days after infection in the right eye. The course of the antibody response in three of the volunteers has been influenced by trachoma vaccine, while titers fluctuated usually between 8 and 16, with an occasional 32 in the three not receiving vaccine.

Skin Tests

Only preliminary studies of skin tests for the diagnosis of trachoma have been completed. An equivalent of a 2% yolk sac suspension of the "purified" inactivated trachoma antigen elicits delayed tuberculin type reactions when 0.1 ml. is inoculated intradermally in persons with various stages of trachoma. The reaction is most intense at 24 hours but persists for at least 48 hours. In some persons, especially those with mild cases, reactions with erythema of greater than 5 mm. have been seen with induration of less than 5 mm. The human volunteers tested prior to receiving trachoma vaccine showed reactions with induration of 10 mm. or greater. No nonspecific reactions were observed. Commercial Frei skin test antigen used as a control did not elicit reactions even in the human volunteers with active infections.

Trachoma Vaccine

With the ability to grow trachoma virus in the laboratory came the possibility of developing a vaccine. It was first determined that trachoma virus could elicit antibodies in animals. Guinea pigs, rabbits, hamsters, mice, and monkeys, when inoculated with both live and formalin-inactivated yolk sac suspensions of trachoma virus, produced complement fixing antibodies. In order to prepare vaccines for human use, purification of the trachoma virus from yolk sac suspension was undertaken. Two strains of the Taiwan trachoma viruses, TW10 and TW29, have been studied. The purification technique used was similar to that used for the complement fixing antigen and has been described in the section on serology. The maximum allowable total nitrogen in typhus vaccine made from yolk sac membranes has been set at 100 mg. per 100 ml. by the United States National Institutes of Health.

A 20% yolk sac suspension of trachoma virus purified by trypsin digestion, three cycles of high-speed centrifugation, and precipitation with polymyxin contains less than 6.5 mg. of nitrogen per 100 ml. This purified material has been inactivated with a 0.04% solution of formaldehyde. Another vaccine has been prepared in which the purified inactivated elementary bodies have been attached to aluminum hydroxide particles by the use of dilute suspensions of gamma globulin (1:200) as an adhesive. Aluminum hydroxide vaccines have contained about 10 mg. of aluminum per milliliter. This vaccine has been studied to determine if a potentiating effect of the immunogenic properties of the virus would occur in the presence of aluminum particles. Because any type of inactivation might alter the antigenic nature of the virus, purified live elementary bodies have been used as vaccine in addition to the two inactivated preparations.

TABLE 7.—*Antibody Response of Monkeys to Trachoma Vaccines*

	No. of Monkeys	Maximum Complement Fixation Titer						
		Neg.	8	16	32	64	128	>256
Formalized vaccine								
Exp. 1*	2	...	...	1	...	1	...	...
Exp. 2†	4	...	...	...	1	3	...	...
Exp. 3‡	2	...	...	...	1	...	1	...
"Live" vaccine								
Exp. 1*	2	...	...	...	...	1	...	1
Exp. 2†	4	...	...	2	1	1	...	...
AL(OH)₃ vaccine								
Exp. 2†	4	...	...	...	2	2	...	...
Exp. 3‡	4	...	...	...	...	1	1	2
Total	22	0	0	3	5	9	2	3

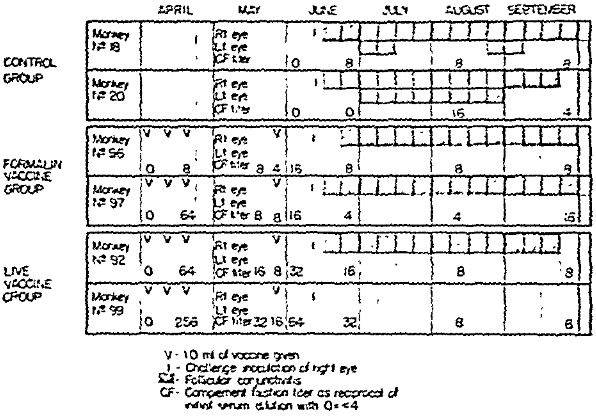
* Crude TW29, 1 ml. of live and 0.5 ml. of formalinized on 0,7,14, and 46 days. Maximum titers, 14 or 23 days, with some fall-off thereafter.

† Purified TW10, 1 ml. on 0,4,8,12, and 33 days, except aluminum hydroxide vaccine, 2.5 ml., given 0 day only. Maximum titers when last measured at 62 and 82 days for all vaccines.

‡ Purified TW29, 1 ml, on 0 day and 0.5 ml. on 27th day. Maximum titers at 42 days when last measured.

Studies in Monkeys.—Antibody responses to these three preparations are presented in table 7. Three experiments have been carried out with various dosage schedules, details of which are appended to the table. In the first experiment, when a nonpurified elementary body suspension of strain TW29 was given at weekly intervals, the maximum titer was reached 14 to 23 days after beginning the experiment and was lower thereafter despite additional vaccine. The eyes of these monkeys were later injected, and that experiment is discussed below. In the second experiment, the three types of vaccine made from purified TW10 virus were tested. After a single 2.5-ml. injection of aluminum hydroxide vaccine, antibody titers increased quickly and persisted at the maximum titer to the time of the last bleeding, 82 days after initiation of the experiment. With the formalinized and live vaccine, either low titer or no antibodies were found until after a booster dose was given. In the third experiment, purified TW29 strain was used and given in two doses one month apart. The best antibody response was in this experiment. All vaccines used in the monkeys were adjusted to contain the equivalent amount of virus in an original 20% yolk sac suspension, less whatever is lost in the purification procedure. It can be seen in table 7 that substantial complement fixing titers (16 to 256) were produced with all vaccines in each experiment. Aluminum hydroxide vaccine produced slightly higher serum titers than the other two materials. No consistent differences were noted between the formalinized and live vaccines.

The four monkeys given crude TW 29 vaccine, along with two controls, were injected intraocularly with 20% yolk sac TW 10 virus nine weeks after onset of immunization. The results of this experiment are summarized in the figure. Follicular conjunctivitis began in the inoculated right eye of the two control monkeys 9 to 11 days after inoculation. Ten days later the infection had spread to the uninoculated left eye in both. In one, monkey 18, the infection in the second eye was mild and disappeared after two weeks but reappeared again for a two-week period during the third month of observation. The two monkeys that had received four 0.5-ml. formalin vaccine injections also developed follicular conjunctivitis in the inoculated right eye, 13 and 18 days after inoculation. A similar response was seen in one, monkey 92, of the two monkeys given four 1-ml. live virus vaccine injections. In none of these three immunized monkeys was there any spread to the uninoculated eye. In one, monkey 99, there was no sign of infection in either eye. This monkey had developed the highest-titer complement fixing antibody response to the vaccine. The intervals used for injection of vaccine were not well chosen, since the maximum antibody titers were not present at the time of inoculation. The CF antibody titers shown in the figure are measured with the purified specific trachoma antigen. When a group trachoma antigen prepared with phenol and heat is used, either no antibodies or only low titers can be demonstrated.



Prevention of monkey trachoma by vaccine.

It should be noted that in this experiment vaccination with strain TW 29 prevented or modified infection with strain TW 10. Similar CF antibody responses in these monkeys have been demonstrated with the use of either purified TW 10 or TW 29 antigens. Bell and co-workers[8] suggested that there are differences among Saudi Arabian trachoma virus strains on the basis of experiments in which toxic death of mice was prevented by prior immunization. TW 10 comes from an area of Taiwan in which mild trachoma is endemic, while TW 29 was isolated in an aborigine area where moderately severe trachoma is endemic, and TW 29 has always grown to higher titers in eggs. Despite these difference, the apparent cross-protection between TW 29 and TW 10 would suggest they are closely related viruses.

Studies in Man.—When trachoma virus vaccines, purified to meet standards for human use, had been prepared, volunteers from the professional and later the technical staff of NAMRU-2 were inoculated with the three types of vaccine (formalinized, aluminum hydroxide, and live) without encountering any reactions except at the site of injection. These reactions were almost eliminated when the formalin content of the vaccines was reduced to an initial 0.02%.

Table 8.—*Antibody Response to Different Inoculations of Three Types of Trachoma Vaccine in Freshmen Medical and Nursing Students*

		Complement Fixation Antibody Titers†									
		1 Mo.				2 Mo.					
Vaccine, Dose*	No. of Persons	0	4	8	16	0	4	8	16	32	64
A, 2 ml., twice...	12	2	2	4	4	..	..	..	4	3	5
F, 2 ml., twice...	13	3	4	4	2	..	1	7	2	3	..
A, 1 ml., twice ..	10	5	3	2	..	2	1	3	3	1	..
F, 1 ml., twice...	14	4	4	4	2	4	2	5	3	..	..
L, 1 ml., twice...	10	3	2	4	1	2	1	5	1	1	..
A, 0.5 ml., twice	11	5	3	2	1	2	1	2	3	2	1
F, 0.5 ml., twice	12	4	2	5	1	2	1	4	4	1	..
F, 0.25 ml., twice	10	4	2	3	1	3	3	3	1	..	..
A, 1 ml., once ..	11	3	2	4	2	3	1	4	3	..	..
F, 1 ml., once ..	9	4	1	1	3	5	1	..	3	..	..
S, 1 ml., twice ..	10	10	..	..	..	10	..	..	..	..	..
S, 1 ml., once ..	10	10	..	..	..	10	..	..	..	..	..

* A = purified elementary bodies attached to aluminum hydroxide particles; F = purified elementary bodies formalinized; L = live purified elementary bodies; S = formalinized saline.

† CF antibody titer in initial serum of 132 persons listed in table was <4 (11 persons in this study with initial antibody not shown). Those groups receiving vaccine twice were given the second injection at the same time as the 1-month bleeding.

A study to test the antibody response to different amounts of the three types of vaccines in humans was arranged in cooperation with faculty members (Drs. O. K. Khaw, H. M. Lin, and F. H. Tai) of the National Defense Medical Center in Taipei. One hundred forty-three volunteer freshmen medical and nursing students at the center were divided into 12 random groups and given different amounts of the three vaccines and placebo material. Three groups received one injection and nine received two injections of vaccine at a one-month interval. There were no generalized reactions to any of the vaccines. These vaccines had been adjusted to contain the equivalent of a 20% yolk sac suspension, and all were made from the same pool of yolk sacs from the 15th egg passage of strain TW 29. The egg infectivity titer of this yolk sac pool was 10^{-4} while that of the final elementary body suspension after purification and prior to inactivation was 10^{-3}. The CF antigen titer of the vaccine was 1:16. CF antibody responses to these vaccines at one and two months after the first inoculation are presented in table 8. Eleven persons with CF antibody in their initial serum are not shown in the table. Two-thirds of the students inoculated with the various doses produced antibodies to the first inoculation. Slightly higher antibody titers were seen with formalin vaccine at one month, but after the second inoculation all groups receiving aluminum hydroxide vaccine showed definitely better responses than the groups receiving similar injections of formalinized or live vaccine. The live vaccine appeared to have no advantage over the inactivated. Antibodies present at one month in the groups receiving a single injection did not change significantly by two months. All students who received 2 ml. of aluminum particle vaccine twice had titers of 16 or greater at two months.

A field study of the ability of vaccine to prevent trachoma in uninfected children of families in which trachoma is prevalent has been undertaken in cooperation with Dr. C. H. Yen, Commissioner of Health of Taiwan, in a rural district on the west coast of the island. In addition, a study of the ability of vaccine to exert a favorable influence on the course of trachoma in children already infected has been started in the same area. About 500 children are involved in these studies. Half the children received the aluminum hydroxide vaccine and half received placebo vaccine. The vaccine used in this study contained the equivalent of an original 40% yolk sac suspension. No serious reactions were observed, although vaccine was given to children as young as 2 months of age. A few of these young children experienced short febrile reactions about eight hours after receiving vaccine. No other general symptoms have been observed.

The theory on which the study of the effect of trachoma vaccine in children already infected with trachoma was undertaken is based on the chronic nature of the infection. While much remains to be learned about the immune response in natural trachoma infection, it does not appear to be effective. Study of the effect of artificially created circulating antibody on the course of trachoma may be worthwhile both for the possible curative effect and to increase knowledge of the immunology of the disease.

In addition to the field study, this theory is being explored in the six human volunteers who have been infected with TW 10 virus. Toward the end of the second month of the experiment, three of the volunteers were started on a series of inoculations with trachoma vaccine in order to study the effect of vaccine on the course of their illness, in comparison with the other three who received placebo injections. Again the identity of the volunteers receiving active vaccines was withheld from the ophthalmologist making the clinical evaluation. Three injections of vaccine at monthly intervals have been received by the volunteers at the time of writing. The antibody response to the vaccination in the volunteers can be seen in table 6. The three volunteers who received vaccine have had a more pronounced rise in titer than the other three. Volunteers 3, 4, and 5, whose conjunctival cell smears contained no inclusion bodies on at least one occasion (see table 3), are the three who received vaccine. They have shown more clinical improvement in their conjunctivitis than the others. These results, while far from conclusive, suggest that the vaccine has had a favorable influence on the course of the infections. Observations on these volunteers are being continued.

Comment

Inclusion bodies in conjunctival cells can be found in only 1% of first-grade school children with trachoma on Taiwan. Since isolation of trachoma virus in other parts of the world in which more severe trachoma is endemic has been associated closely with inclusion-positive cases,[13] the low rate of such cases on Taiwan probably accounts for the low virus isolation rate here.

The reproduction of disease with the clinical and laboratory characteristics of trachoma in six human volunteers with one of the Taiwan trachoma viruses adds valuable evidence in proving that the elementary body viruses grown in egg yolk sac from eye specimens of trachoma patients are in reality causal agents of trachoma. It was of interest that the human eye was infected with a higher dilution of trachoma virus than that which infected eggs. Human infections with yolk sac trachoma viruses have been reported both in volunteers[14] and through laboratory accident.[15] However, in only one of these infections, and that in a volunteer with both eyes enucleated, had the process progressed to the chronic cicatrized changes typical of trachoma. Collier[13a] has stated that in an unpublished experiment pannus has occurred in a volunteer.

The fact that conjunctivitis caused by type 4 adenovirus in a human volunteer could be clinically differentiated from trachoma virus infection, was of interest because in the experiments by Feng and co-workers[16] adenoviruses caused eye disease indistinguishable from that caused by conjunctival scrapings of trachoma patients.

Growth of trachoma virus in the allantoic cavity of the egg or in tissue culture would facilitate the production of vaccine. To date, there have been no reports of propagation of the virus except in the yolk sac. Gordon and co-workers[17] grew one of the Taiwan trachoma strains through one development cycle in tissue culture of the entodermal cell of the chick embryo; however, the virus has not been grown in quantity.

Isolation techniques are not yet sensitive enough to provide a useful diagnostic aid in trachoma, but the development of a specific antigen offers great hope for better laboratory diagnosis. A surprising finding was that "purified" elementary bodies of trachoma virus, when employed as CF antigen, measured antibodies in human cases and infected monkeys not measured by antigens enhanced by phenol and heat. This is the opposite of what occurs with psittacosis and lymphogranuloma venereum. It would appear that trachoma infection produces specific antibodies and few or no group antibodies. Although the trachoma viruses are related to the psittacosis–lymphogranuloma venereum group, they clearly stand apart from the other human viruses of that group. Why only one-fourth to one-third of first-grade school children with trachoma have measurable antibodies is not clear, but this may be related to the mild trachoma prevalent on Taiwan. It remains to be seen how useful the CF test will be in diagnosis, but already it has provided evidence that many children have trachoma infections who have been diagnosed as having nontrachomatous chronic follicular conjunctivitis, usually because no corneal disease is found. While the skin test for diagnosis of trachoma appears to be promising, considerably more experience is needed before the extent of its usefulness can be fairly assessed.

There are many theoretical and practical problems which suggest that great caution should be used in evaluating the potentialities of prevention of trachoma by immunization. It is well known that the psittacosis–lymphogranuloma venereum group sets up foci of chronic infection in animals and birds. Natural immunity after infection is often unable to rid the body of these viruses completely and relapses occur. Persons with "cured" trachoma are susceptible to reinfection or relapse. Trachoma is an infection of the superficial cells of the eye, and how well humoral antibodies will protect such tissue is unknown. Past studies in animals on vaccine protection against viruses of the psittacosis–lymphogranuloma venereum group have been disappointing because, frequently, protection depends on the route of inoculation. Although it has been possible to protect mice by prior vaccination against toxic death from trachoma virus, antigenic differences among trachoma strains have been reported,[8] which raises the possibility of a multiplicity of immunologically different trachoma strains.

In spite of these problems, the results of the preliminary studies with trachoma vaccines provide some reasons for optimism. Trachoma vaccine appears to be entirely safe; even noninactivated virus given intramuscularly was innocuous. Antigens specific for trachoma have been prepared. Purification of the virus enhances its ability to react with specific antibody. Vaccine made from suspensions with relatively low titers of virus produced in humans an antibody response equivalent to that found in natural trachoma. Attaching the elementary bodies to aluminum particles improved the antibody response. Circulating antibody measured by the CF test appeared to have a protective effect in monkey eyes against infection with the trachoma virus.

Because of the paucity of information about the immunology of trachoma, the present field studies are designed for long-term follow-up investigation, in order to obtain basic information on the immunology of the disease as well as data on the protective or curative effect of vaccine.

Summary

Five trachoma viruses have been isolated from persons on Taiwan with use of the yolk sac of chick embryos. They are morphologically and serologically related to the psittacosis–lymphogranuloma venereum group. So far, these viruses have been grown only in the egg yolk sac, monkey eye, and human eye. Trachoma has been reproduced in six human volunteers with one of the Taiwan virus strains. The virus has been shown to be sensitive to the action of penicillin, oxytetracycline, chloramphenicol, a sulfonamide, and a nitrofurazone compound. A purified specific trachoma antigen has been prepared that measures complement fixation antibodies in the serum of trachoma patients and gives promise as a skin test antigen for diagnosis. Trachoma has been shown to differ from psittacosis and lymphogranuloma venereum in that infection with trachoma virus produces mainly specific antibodies which do not react with group antigens. The purified virus antigen has been used as a vaccine and has produced significant antibody response in monkeys and humans. Monkey trachoma has been prevented or modified by vaccine. Over 450 humans have been given trachoma vaccine without untoward reactions. Evidence suggesting a curative effect of the vaccine was obtained in the human volunteer infections.

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READY-MADE MIXTURES OF ANTIBIOTICS.—It is discouraging and disquieting that, in spite of repeated expositions of the defects of the fixed combinations and the potential or actual dangers of their application, they are still being prescribed in sufficient quantity, both here and abroad, to encourage the manufacturers in continuing their production and in promoting their use. It cannot be too strongly emphasized that the best interest of the individual patient is served and the least harm done when antibiotics are prescribed, each in its optimum dosage and only for infections in which it is specifically indicated. Their possible curative and life-saving properties will also best be preserved for other patients if they are always used only in this manner.—Antibiotics in Fixed Combination, Editorial, *New England Journal of Medicine*, Feb. 4, 1960.

CURRENT CONCEPTS OF PNEUMOCONIOSES–CLINICAL ASPECTS

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The diagnosis of silicosis should be made only after scrupulous application of three diagnostic criteria: the medical history, the roentgenographic pattern, and the results of physical, physiological, and laboratory examinations. The consequences of basing a diagnosis of silicosis on roentgenographic findings alone is illustrated by the case history of a man who filed a claim for compensation after a chest x-ray revealed diffuse, irregular nodulation in the lung shadows. Reexamination after 10 months of unemployment and worry showed that the abnormality was no longer present, and because of the initial mistaken diagnosis the real cause was never determined. The importance of tobacco smoking as a factor in supposedly occupational respiratory disease needs to be determined. Concern over problems of compensation should not divert attention from the equally important problem of rehabilitation.

Present-day opinions on the clinical aspects of the pneumoconioses seem so varied and diverse that one wonders at times if there ever will be unanimity of thought in this field. These opinions run the gamut from complete disability with the most minimal and benign pneumoconioses to little or no impairment of lung function with some of the most advanced conglomerate fibroses. Medical opinions on the cause and effect relationship in the "dust diseases" occasionally are so inconsistent that it seems we scarcely have progressed beyond the "melanosis" of the early French anatomists [1] or the "black expectoration" of William Thomson [2] of Edinburgh over a century ago.

Definition of Pneumoconiosis

First of all, let us consider the term "pneumoconiosis" which Zenker [3] coined in 1867 as "pneumonokoniosis" (the "no" was dropped at the 1930 International Conference).[4] It means only "dust retained in the lungs," without implication of any reaction to the dust. While some dusts, notably crystalline-free silica and asbestos, do cause a fibrous tissue reaction in the lungs, it is now recognized that numerous others are quite inert when retained in minimal to moderate concentrations. Yet, numerous modern textbooks and dictionaries still define pneumoconiosis as "fibrosis of the lungs due to dust exposure," without consideration of those dusts which are essentially nonfibrogenic.

It is necessary to understand that all men have pneumoconiosis, because we retain varying amounts of atmospheric dust in our lungs. This usually is not visualized roentgenographically, because the dust either is not localized in sufficient concentration or is not sufficiently dense, so that our chest films are interpreted as showing "healthy lungs." Were the retained carbon in our lungs of the same density as iron, radiologists would diagnose "pneumoconiosis" in most of us. It is apparent, therefore, that one must understand who is using the word "pneumoconiosis." To the pathologist it means "retained particulate material in focal areas in the lungs or fibrous tissue reaction to a fibrogenic dust," and to the radiologist it means "a pattern of generalized nodular shadows, with or without associated conglomerate shadows." To other physicians, particularly chest specialists, who are vitally interested in the effect of all forms of atmospheric pollution on the lungs, it must be a combination of both concepts plus a detailed understanding of which dusts may or may not be harmful under which conditions of dustiness and which association of the dust with other factors may change the primary pattern.

Clinical Diagnosis

From a purely clinical standpoint, therefore, each patient who presents himself for evaluation either for a job in a "dusty" trade or because of symptoms referable to the chest requires the most detailed study before a diagnosis can be made and advice given. Unless roentgenographic changes are properly evaluated and sound clinical judgment is used, irreparable psychological harm can be done to the worker. I repeat here what I have stated on numerous occasions [5]: Well-meant but overexaggerated medical advice to workers in some of the more common dusty trades has resulted in more disability than has the lung pathology itself. Such fear-induced disability is just as real to the patient as are the symptoms resulting from advanced silicosis.

To prevent these unfortunate misdiagnoses, the well-known triad of diagnostic criteria must be scrupulously applied in almost every case which presents itself, namely (1) taking of a medical history, (2) roentgenographic pattern, and (3) physical, physiological, and laboratory findings. A detailed medical and occupational history is fully

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as important as the other two criteria, and a definitive diagnosis never should be made from the roentgenogram alone, no matter how tempting it may be to do so. A case report will serve to illustrate the importance of knowing the full details of a case of occupational dust exposure.

Report of a Case.—A 28-year-old man presented himself to his physician in August, 1953, with a rather marked "chest cold" accompanied by a slight fever and some shortness of breath. A chest x-ray (fig. 1, *right*) revealed a diffuse and somewhat irregular nodulation, which was diagnosed by the physician as silicosis when he was told that his patient was an enameler. When penicillin therapy gave no results and the nodulation was still present three months later (fig. 2, *left*), the physician was firmly convinced of his diagnosis and advised the patient not to return to his job. A claim for compensation was filed, and the patient appeared in my office for evaluation. By that time, some 10 months later, all of the nodulation had disappeared (fig. 2, *right*). While the precise cause of the nodular infiltration never was established (it could have been either a viral pneumonitis or sarcoidosis with spontaneous remission), the patient's physician would not have been misled had he made a more detailed inquiry into the man's occupational history. He would have found that there had been only minimal dust exposure, for 16 months, to a vitreous enamel powder which cannot cause silicosis, because all the silica is in a combined state and is not fibrogenic. The enameler is back on his regular job and has had no recurrence of whatever disease he had in 1953.

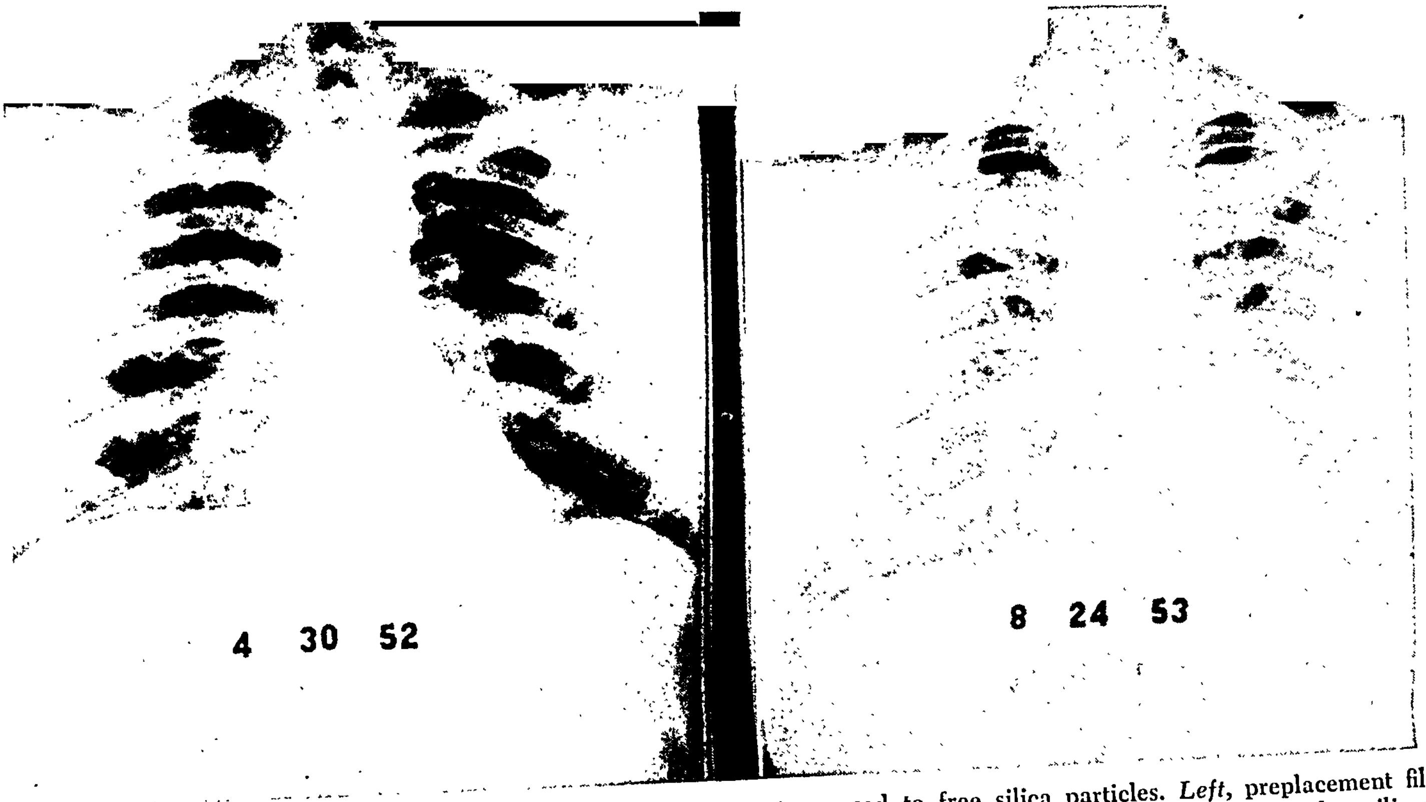

Fig. 1.—Mistaken diagnosis of silicosis in enamel workers not exposed to free silica particles. *Left*, preplacement film, 4/30/1952, showing healthy lungs. *Right*, film made 8/24/1953, showing irregular nodular infiltration misdiagnosed as silicosis.

Diagnosis in Grinders

A few other occupations, of which grinding is an outstanding example, need especially detailed inquiry. The early British literature on silicosis is dominated by reports of the cutlery grinders of Sheffield[6] who, in those days, used sandstone wheels exclusively. In the United States the sandstone wheels had, by 1930, been largely replaced by artificial abrasives, such as silicon carbide (Carborundum or SiC) and aluminum oxide (Aloxite or Al_2O_3). Both of these abrasives are quite inert when retained in the lungs, even in moderately heavy concentrations, and it appears from the recent animal studies by Gross[7] and others[8] that they may be fibrogenic only when inhaled in extreme concentrations or when associated with tuberculoprotein. At any rate, they do not result in any roentgenographic nodulation resembling silicosis. Yet, although such nodulation is seen roentgenographically in many grinders, it is misdiagnosed as silicosis because care was not taken to obtain a detailed occupational history. It is true that, if the castings being ground still have baked molding sand on their surfaces, the grinder will have some silica exposure, and this fact must be elicited in the occupational history. However, if the castings or steel objects being ground have no sand scale on their surfaces and if the work is being done in an area in which there is no silica dust dissemination, then such a grinder can be exposed only to iron dust, plus a minimal amount of the artificial abrasive dust, from the grinding wheel. Iron dust, we now know, can be retained in focal areas in the lungs in sufficient concentration to be visualized roentgenographically as nodulation. This sometimes is difficult to differentiate roentgenographically from silicosis, unless all details of the occupational environment are known. When it is certain that there was no free silica exposure, such as in the case reported next, then there is no room for doubt as to the precise cause of the nodulation.

Report of a Case.—A grinder of ball bearings used aluminum oxide wheels without exhaust ventilation in an area in which there was no silica dust dissemination. Yet, he was given a diagnosis of silicosis and advised to leave his job. The fine nodular pattern throughout both lungs and the normal root shadows that are visible in figure 3 are noteworthy. The latter finding alone tends to rule out silicosis as the cause of the nodulation. This man, as well as other ball-bearing grinders, had no chest symptoms or impaired lung function. He still is working at his regular job. His physician did not realize that there is nothing inherent in an occupational history which proves by itself that a silicosis hazard does or does not exist.

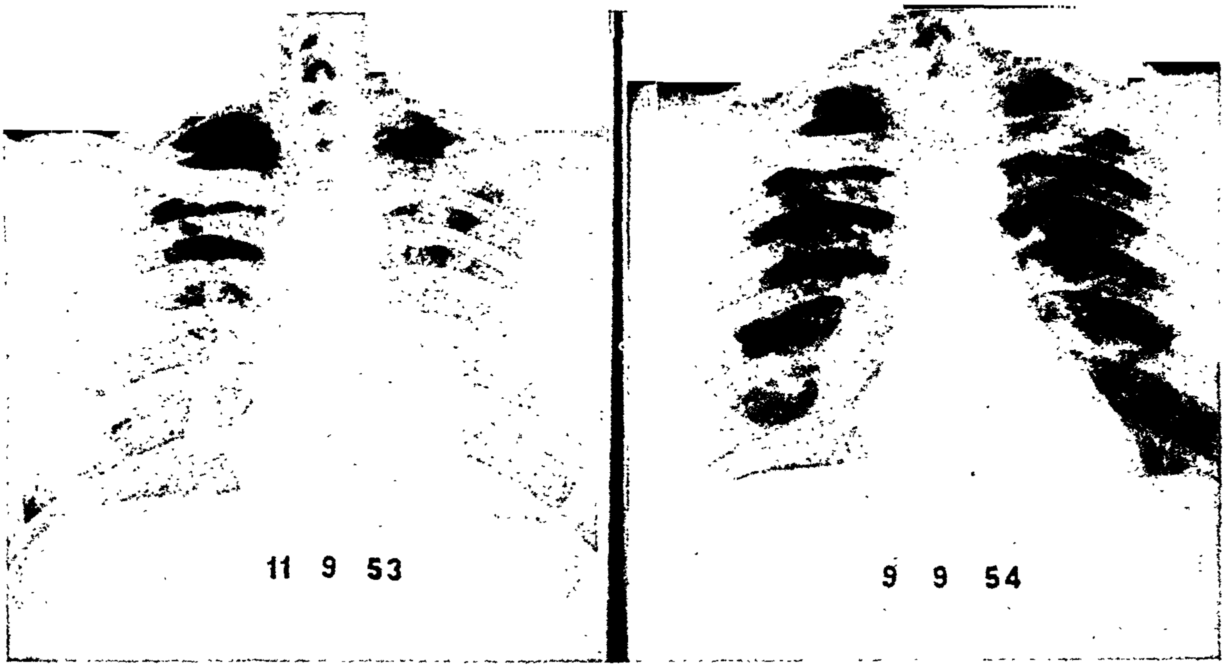

Fig. 2.—Same patient as in figure 1. *Left,* film made 11/9/1953, showing practically unchanged nodular infiltration. *Right,* complete clearing of infiltration by 9/9/1954.

To obtain the additional information on the exact environmental factors, it sometimes is necessary to go beyond what the patient himself can give. Most workers in foundries, for example, do not know what percentage of the dust they inhale is free silica. This information is at times obtainable only from detailed dust surveys undertaken by industrial hygiene engineers. Most industries with dust hazards have had such surveys from time to time, and their medical directors or consultants have this information. Those I know always welcome calls from family physicians who want this additional information before they make a definitive diagnosis. A free interchange of such environmental data is most desirable, and more and more industries welcome the opportunity to give this information to the family physicians of their employees.

Significance of Smoking Habits

In a paper of this length it is impossible to cover all points in the clinical aspects of the pneumoconioses. The symptoms and physical findings must be passed over completely, but I want to mention briefly a most important item to be elicited in the history—the smoking habits of the patient. Increasing numbers of lung-function investigations [9] show direct correlation between excessive smoking and impairment of the ventilatory capacity of the lungs. The smoking history must be complete from the time of onset, with an estimate of total consumption through the years and of whether there are symptoms of cough and sputum attributable to the smoking. There is increasing evidence that smoking per se may be a major factor in the development of bronchitis, bronchiolitis, and obstructive emphysema. Clinical investigations of the effect of certain dusts on the lungs no longer can disregard the smoking habits of the workers included in the study.

Epidemiologic studies in large population groups on the incidence of recognizable emphysema at the various age levels, in smokers vs. nonsmokers, and in workers with and without occupational dust exposure are sorely needed. British colleagues are, at the time of writing, completing such a large-scale study, in the coal-mining town of Staveley in Derbyshire, to determine if coal miners and ex-miners have more measurable lung impairment, especially bronchitis and emphysema, than do foundrymen and others in the same town. They have included the smoking habits of each subject in the study. Preliminary findings suggest that heavy tobacco smoking is a major cause of chronic lung disease, and that it no longer is valid to draw conclusions on the effects of occupational dust and air pollution exposures without also considering the smoking habits of those exposed.[10] Until we have more definite knowledge of the effect of all forms of atmospheric pollution on the lungs, a discussion of the clinical aspects of the pneumoconioses must remain inconclusive. With simple nodular silicosis, for example, I can make only the general statement that my observations[5] suggest that, in the case of most such workers, there are no symptoms referable to the lungs and no significant reduction in the ventilatory capacity of their lungs. The occasional patient with a case of diagnosable bronchitis and emphysema must be evaluated in the light of the many other causes of bronchitis and emphysema. In many such patients with minimal silicosis, it is unsound to conclude that their silicosis was the major cause of the emphysema. Such unrealistic thinking has, in my experience, been responsible for a complete neglect of the patient who needs a treatment regimen directed at the underlying cause of the emphysema.

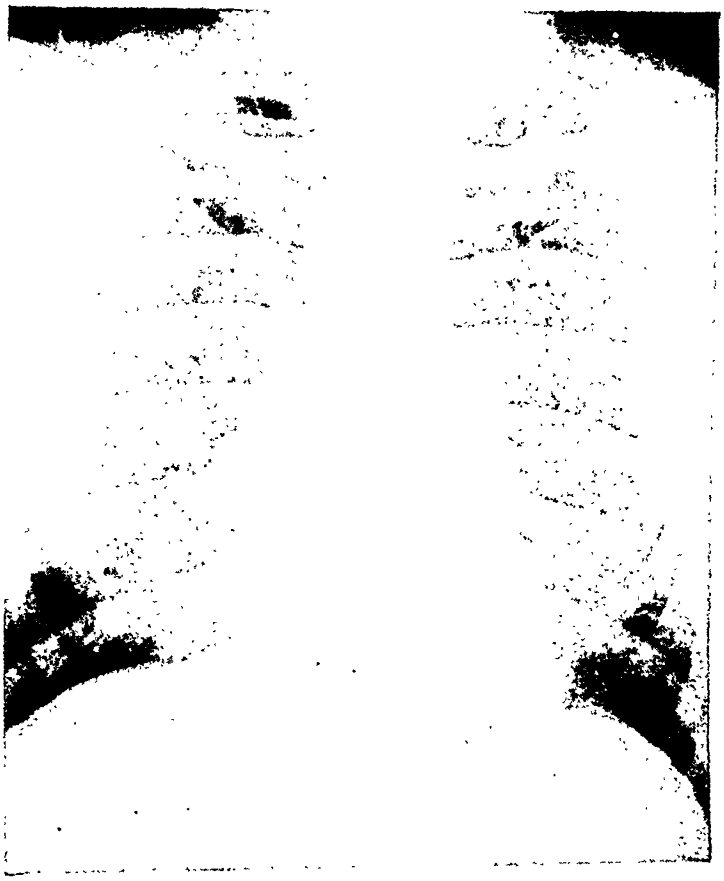

Fig. 3.—Mistaken diagnosis of silicosis in ball-bearing grinder using artificial abrasive wheels, exposed not to silica but to iron dust. Film shows fine nodular pattern and normal root shadows characteristic of iron retention or siderosis.

Summary and Conclusions

Clinical evaluation of the pneumoconioses requires a new approach focused on relieving whatever symptoms and fears a patient may have and taking steps to prevent his pneumoconiosis from progressing or becoming complicated by other diseases. Too many clinical evaluations today are concerned only with the determination of whether the patient has or does not have an occupational disease for which he may receive compensation. This is one of the most neglected areas in the whole field of rehabilitation. The worker who has symptoms or thinks he had symptoms from his pneumoconiosis needs help. He deserves the same consideration that is given to other patients, which is to treat him with the proper medicinal, physical, and psychological therapy which will rehabilitate him to maximum gainful employment consistent with his impairment. Those with real impairment due to their pneumoconiosis and after maximal rehabilitation are entitled to receive compensation for whatever loss of earning capacity they may have suffered as a result of this impairment. It is the physician's duty to make these determinations impartially and to give his opinion on the degree of this impairment, but concern for the patient should not end there. At this point he needs the most optimistic advice one can give him to preserve his sense of well-being and usefulness in life. Only then has the physician done all he can for the patient with pneumoconiosis.

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PULMONARY FUNCTION IMPAIRMENT IN PNEUMOCONIOSES

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The reliability of chest roentgenograms in the appraisal of pneumoconiosis was tested in 98 men actively working in industry with diatomaceous earth. Functional impairment was evaluated by applying a variety of physiological tests, and the results of pulmonary function tests in three men with severe impairment are given in detail. The functional tests made it possible to distinguish restrictive, obstructive, and other factors in the total impairment of respiration. They also showed a low degree of correlation with the results of chest roentgenography. Positive findings of neither roentgenographic study alone, timed vital capacity alone, nor any other single functional test give a sufficient reason for removing the worker from his job. Accurate testing of pulmonary function should be done more extensively, and serial follow-up studies are necessary in handling the individual case.

Pulmonary function is evaluated on the basis of the ability of the lungs to supply oxygen to and remove carbon dioxide from the blood adequately during rest and exercise. The large pulmonary reserve in man often obscures and delays clinical and roentgenologic detection of the early pathological changes of fibrosis and emphysema before clinical symptoms are prominent. In most cases of pneumoconiosis with dyspnea the disability is due to fibrosis and emphysema. The major physiological changes in the pneumoconioses consist of impairment in alveolar aeration on the ventilatory side, hypoxia and hypercapnia from disturbance in the transport of oxygen and carbon dioxide in the lung, and decreased pulmonary-blood flow during exercise from lack of expansibility of the pulmonary vascular bed.[1]

The total vital capacity, the timed three-second vital capacity, the maximum breathing capacity before and after administration of a bronchodilator, and the shape of the tracing on the record constitute the important measurements obtained from a spirogram record, which is necessary for precise evaluation of the ventilatory status. The residual air can be determined quickly and accurately with use of the helium closed-circuit-dilution method.[2] The use of the nitrogen meter for nitrogen washout on oxygen breathing constitutes the best test for evaluation of intrapulmonary mixing defects.[3] The severity of the emphysema can be evaluated from the measurement of the volume of the residual air and the ratio of the residual air to total lung capacity, with tests of intrapulmonary mixing and the spirogram data. These tests provide information with respect to the ability of the individual person to move air down to the alveolar level where the oxygen can be taken in and the carbon dioxide blown off. The ventilatory abnormalities or the inability to aerate the alveoli adequately represent a major difficulty in pneumoconiosis.

Emphysema and fibrosis in various degrees occur in patients with pneumoconiosis.[4] The total vital capacity may be normal or reduced. The timed vital capacity is decreased in the presence of emphysema (usually of the obstructive type) significantly below the total vital capacity. The maximum breathing capacity is usually decreased farther below the predicted value than is the timed vital capacity. When fibrosis is the dominant aspect, without significant emphysema, as in some patients with asbestosis, the maximum breathing capacity may be increased much above the timed vital capacity or the total capacity, and exhalation time is normal. The residual air is increased in varying degrees, and nonuniform air distribution is present. Some alveoli are normally ventilated, others are poorly ventilated, and some are not ventilated at all, since air cannot pass the obstructions of the bronchi by mucus and secretions, bronchospasm, infection, edema, or fibrosis. The nonventilated alveoli may have blood perfusion in the capillaries but no gas exchange. Bronchospasm is a common occurrence and can usually be demonstrated by measuring the maximum breathing capacity before and after a bronchodilator treatment with a mixture of epinephrine and chlorobutanol (Vaponefrin) or isoproterenol (Isuprel) hydrochloride. The lung volume changes with decreased elasticity, and compliance increases the work of breathing. The use of a ventilation factor has been found satisfactory for simple objective expression of the ventilatory defect.[5] The ventilation factor is the average of the timed three-second vital capacity, the maximum breathing capacity, and the residual percentage of total lung capacity, all expressed on a basis of the predicted normal value. If the ventilation factor is normal (100%) then the alveoli are adequately aerated, but if it is decreased to as low as 25%, dyspnea is usually present even at rest.

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The adequacy of oxygen and carbon dioxide transport in the lung is evaluated primarily from the arterial blood oxygen saturation at rest and with exercise. The level of the carbon dioxide content is important, especially when elevated. If hypoxia is present at rest or with exercise on air breathing, simple tests are used to identify the cause. The changes in the arterial blood oxygen saturation occurring during (1) intermittent positive-pressure breathing with compressed air only and (2) graded levels of high-oxygen breathing (32 to 40% oxygen and 100% oxygen), with both rest and exercise,[6] provide information about the factors producing the hypoxia. Arterial hypoxemia occurs in the presence of poorly ventilated alveoli, the perfusion of blood through nonventilated areas (such as the shunts from right to left that are present in fibrosis and atelectasis), large shunts from right to left (present in congenital heart disease and arteriovenous fistula), and alveolar capillary membrane block.

TABLE 1.—*Pulmonary-Function Measurements in Three Types of Pneumoconiosis with Severe Function Impairment*

		Pulmonary Function Measurements		
Case No.*		1	2	3
Vital capacity, supine, observed, ml.		2,265	3,610	1,835
predicted, %		52.1	95.4	56.8
Timed vital capacity, observed, ml.		1,391	1,780	1,837
predicted, %		32.0	46.7	56.8
Maximum breathing capacity, observed, liter/minute		25.6	31.4	80.2
predicted, %		21.9	26.7	73.7
After use of broncho-dilator, observed, liter/minute		33.1	36.2	101.0
Alveolar N_2 after 7-minute O_2 breathing		2.78	2.78	1.22
Residual air, observed, ml.		3,210	2,094	1,359
predicted, %		221.4	128.1	126.1
Total lung capacity, observed, ml.		5,475	5,731	3,194
predicted, %		91.4	105.2	74.1
Residual of total lung capacity, %		58.6	36.5	42.5
Ventilation factor, %		32.2	51.9	63.1
Arterial blood	Rest	89.5	95.0	93.8
Air	Rest, IPPB†	91.0	97.3	96.5
Oxygen, %	Rest, 100	97.3		99.6
Saturation, air	Exercise	83.7	85.8	82.0
	Exercise, IPPB†	...	...	89.5
Oxygen, %	Exercise, 32	...	...	90.5
	Exercise, 40	92.2	...	...
CO_2 content Vol. %	Rest	60.3	52.0	45.5
	Exercise	56.9	49.9	45.8
Minute ventilation Liter/sq.m. B.S.A.‡	Exercise	8.14	9.11	10.0
Oxygen uptake, ml./minute/sq.m. B.S.A.‡	Exercise	331	339	403

* Case 1: diatomite workers for 3 yr., age 55 yr., height 176.5 cm. Roentgenographic changes: nodular, 3rd stage; confluent, 3rd stage. Case 2: hard-coal miner for 37 yr., age 61 yr., height 172 cm. Roentgenographic changes: nodular, 3rd stage. Case 3: asbestos worker for 37 yr., age 58 yr., height 150.2 cm. Roentgenographic changes: linear, accentuated at both bases.

† IPPB = intermittent positive pressure breathing.

‡ B.S.A. = body surface area (calculated).

Decreases in the arterial blood oxygen saturation are a common finding in pneumoconiosis.[7] The resting saturation is frequently in the low 90% range at sea level. With mild exercise the saturation may decrease 5 to 10% or more in some cases, increase a few percentiles in others, or show no change. The decrease in the saturation is due primarily to the presence of poorly ventilated alveoli perfused with blood and to the perfusion of blood through nonventilated areas in which air flow is blocked from descending to the alveolar level where gas exchange can occur. The latter situation actually constitutes small shunts at the alveolar level. The increased cardiac output during exercise usually opens up more capillaries in areas where the ventilation-perfusion abnormalities are most extensive. A 32 to 40% oxygen-breathing gas will not obscure this shunt even with exercise,[6] but breathing of 100% oxygen does obscure it, especially at rest, because the oxygen dissolved in the plasma is markedly increased. The use of 100% oxygen breathing can be used to rule out large right-to-left shunts but not small ones.[6]

The 32% oxygen-breathing gas increases the inspired oxygen pressure (pO_2) over 70 mm. Hg and is adequate to overcome an alveolar capillary membrane block, if this is the significant factor producing the hypoxia. Intermittent positive-pressure breathing improves the ventilation in the poorly aerated alveoli, so that the oxygen partial pressure becomes more nearly normal and the blood that perfuses these alveoli approaches normal saturation. Most patients with pneumoconiosis associated with hypoxia show an increase in the arterial blood oxygen saturation on intermittent positive-pressure breathing of compressed air only. Physiological studies show that the improved saturation results from more uniform alveolar aeration.[8] The deeper breathing with exercise also provides more uniform alveolar aeration in some cases, with a resultant increase in the arterial saturation. Physiological studies on the nature of the hypoxia in pneumoconiosis of both soft-coal and hard-coal miners, in silicosis, in diatomite pneumoconiosis, in asbestosis, and in pottery workers' pneumoconiosis reveal the cause to be due primarily to two factors, (1) poorly ventilated alveoli and (2) the perfusion of blood through nonventilated areas. The presence of an alveolar capillary membrane block has not been found to be a significant factor in the pneumoconioses. Even in interstitial pulmonary fibrosis and other restrictive conditions of the lungs, hypoxia results from perfusion of blood through nonventilated areas and not from an alveolar capillary membrane block.[6]

In table 1 data are presented on three types of disabling pneumoconiosis. In cases 1 and 2 there is obstructive emphysema and impairment in intrapulmonary mixing. In the patient with asbestosis (case 3) the obstructive factor is absent and emphysema is not a significant factor in the disability. The restrictive condition is dominant in case 3 and the patient cannot take a deep breath. The maximum breathing capacity is much greater in case 3 than the timed vital capacity as a percentage of the predicted normal. The intermittent positive-pressure breathing on air improves the resting saturation in the patients in all three cases. The decrease in the exercise saturation was not corrected on high-oxygen breathing (32 to 40% oxygen) for the patients in cases 1 and 3, and this indicates the perfusion of blood through nonventilated areas, rather than the existence of an alveolar capillary membrane block.[8] The coal-mining patient (case 2) illustrates a common finding in this type of pneumoconiosis: the dominant influence of fibrosis with secondary emphysema. In case 1 the emphysema is dominant to the fibrosis, and in case 3 the fibrosis is primary, with insignificant emphysema. The exercise oxygen uptake was markedly decreased in all patients, indicating the inability to expand the pulmonary vascular bed and the presence of increased pulmonary vascular resistance.

In a case in which the exercise oxygen uptake is decreased, in the presence of adequate minute ventilation, abnormalities in the pulmonary blood flow are indicated. The patient is unable to increase the pulmonary blood flow in an amount corresponding to the degree of exercise given. The decreased exercise oxygen uptake indicates indirectly the presence of increased pulmonary vascular resistance, without it being necessary to catheterize the right heart and measure mean pulmonary artery pressure and cardiac output. The inability to expand the pulmonary vascular bed represents a common abnormality in pneumoconiosis in the presence of fibrosis and emphysema. In some patients, one or two liters may be the maximal increase in cardiac output with exercise.

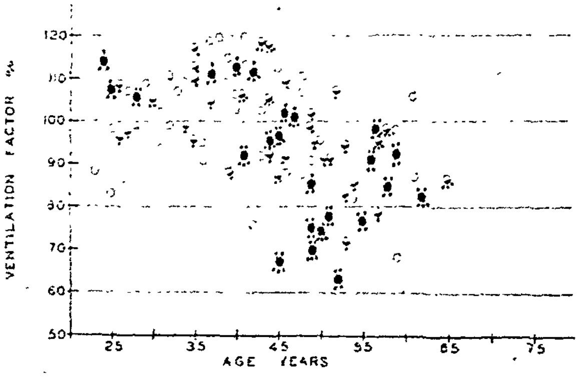

Fig. 1.—Survey of workers in diatomite industry: correlation of ventilation factor as percentage of predicted normal value with age in years and appearance of x-ray film in 98 subjects still working in diatomite industry. Number of dots attached below circle indicates stage of nodularity on x-ray film (*1*, *2*, or *3*), and number of dots above indicates degree of confluent change (*1*, *2*, *3*, or *4*). Open circles indicate negative roentgenographic findings. Ventilation factor represents average of timed vital capacity for three seconds, maximum breathing capacity, and residual percentage of total lung capacity, all expressed on basis of predicted normal value. No correlation between ventilation factor and change in roentgenogram was apparent.

Pulmonary function studies have been obtained on 98 diatomaceous earth workers who are still on the job in this industry and have no major complaints. The workers were selected by the United States Public Health Service in connection with their survey of the diatomite industry[9] to provide a representative cross section of patients with this type of pneumoconiosis. The roentgenographic classification used by the Public Health Service described findings as normal, linear-nodular, and nodular-confluent. The linear and nodular changes were grouped together, and the classification was simplified, as follows. LN_1: suspicious for linear-nodular changes; LN_2: definitely abnormal linear changes, nodular changes, or both, involving an area less than the equivalent of two quadrants of the lung field; LN_3: linear changes, nodular changes, or both, involving more than one-half the total lung area or extending to or nearly to the periphery of both lung fields bilaterally; C_1: confluent shadows of uncertain or ambiguous significance, superimposed on any of the foregoing; C_2: massive confluent opacities definitely present, extending over less than the equivalent of three anterior rib spaces on either side; C_3: *massive confluent opacities definitely* present, extending over the equivalent of three or more anterior rib spaces on either side; C_4: massive confluent opacities, associated with gross distortion of the pulmonary anatomy.

The ventilation factor as a percentage of the predicted normal value was correlated with the roentgenographic change and the age of the patient (fig. 1).[10] In 41 patients the ventilation factor was 100% or more above the predicted value, and in 32 it was slightly decreased (in insignificant degree), which indicates that in 73 of the 98 patients studied alveolar aeration was normal. In 14 patients the ventilation factor was decreased slightly (80 to 90%) and in 11 moderately (60 to 80%). Although 7 of the 11 patients with a moderate decrease in the ventila-

Table 2.—*Correlation Between Pulmonary-Function Studies and Roentgenographic Classification of Pneumoconiosis in 500 Coal Miners*[1]

	No. of Cases	Roentgenographic Stage†			
		N to B	1st	2nd	3rd
Degree of Function Impairment*					
Slight	85	10	16	28	31
Moderate	163	15	21	35	92
Severe	173	10	20	25	118
Very severe	79	2	16	15	46
Degree of Pulmonary Emphysema[5]					
None	37	6	3	13	15
Slight	136	8	18	35	75
Moderate	164	13	19	23	109
Severe	108	7	19	19	63
Very severe	55	3	11	13	25

* Over-all evaluation based on complete battery of tests as described (Motley[5]).

† N is normal; B is borderline, increased peribronchial markings; 1st stage, slight fine mottling of parenchyma and increased size and density of hilar lymph nodes; 2nd stage, typical nodular round and oblong shadows of soft, even density from 2 to 6 mm. in diameter; 3rd stage, shadows more than 6 mm. in diameter and coalescence forming aggregates.

tion factor had nodular-confluent changes, 14 patients demonstrated a normal ventilation factor and nodular-confluent roentgenographic changes. There was no significant correlation between the roentgenographic changes and the ventilation factor (fig. 1). Similar comparisons for the three-second timed vital capacity, maximum breathing capacity, and residual air as a percentage of the predicted normal value failed to reveal any significant correlation. Thus, the presence of extensive changes on the x-ray film is not necessarily associated with a decrease in the timed vital capacity or the maximal breathing capacity below the predicted normal value. Furthermore, the residual-air volume may be normal in the presence of nodular and confluent roentgenographic changes. Similar observations have been made in coal miners, as has the lack of correlation between the roentgenographic changes and the severity of the emphysema present (table 2).[1]

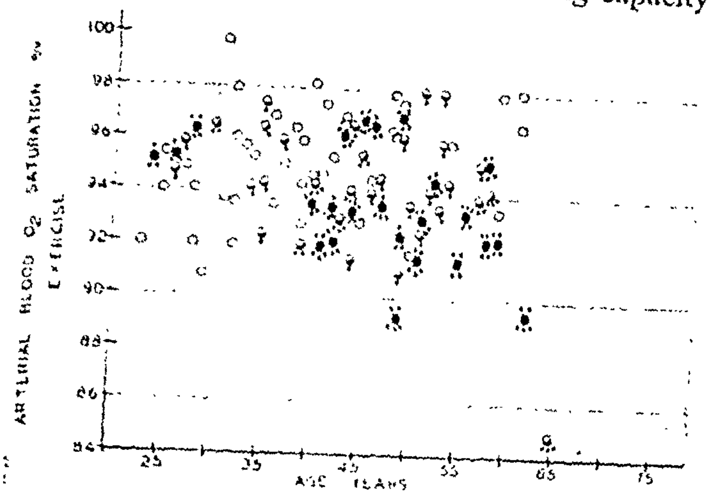

Fig. 2.—Survey of workers in diatomite industry: correlation of step-up exercise arterial blood oxygen saturation with age in years and roentgenographic appearance. Individual cases are represented on chart as described in fig. 1. Exercise arterial blood oxygen saturation was above 90% in all but three cases. No correlation of exercise arterial blood oxygen saturation with change in x-ray film was apparent.

The arterial blood studies at rest in the diatomite workers reveal a significant reduction below the normal value of 96% in many of the cases, usually of a moderate degree between 92 and 94%. However, with exercise, there was an increase in the saturation as compared to the resting saturation in a considerable number of patients. The exercise arterial blood oxygen saturation on air breathing was correlated with the roentgenographic change and the age in years (fig. 2). In three cases the arterial saturation was less than 90% and in six cases between 90 and 92%. Of 31 patients with a normal exercise saturation of 96% or more, 17 had negative, 9 had nodular, and 5 had nodular-confluent roentgenographic changes. No significant correlation was noted between the exercise arterial blood oxygen saturation, the roentgenographic stage, and the age of the worker (fig. 2). Intermittent positive-pressure breathing on compressed air resulted in a normal saturation of 96% or more in most of the diatomite workers, which indicates that the decrease noted in the resting saturation is primarily due to the presence of poorly ventilated alveoli.[10] In patients with a decrease in saturation on air breathing during exercise, the use of a high oxygen-breathing gas (32% oxygen) did not restore the normal level, as would be expected if the major difficulty were an alveolar capillary membrane block. The studies indicate that the presence of perfusion of blood through nonventilated areas is the major difficulty producing hypoxia. The absence of evidence for the existence of an alveolar capillary membrane block was a consistent finding.

The exercise oxygen uptake was significantly decreased in 26 of the diatomite workers, distributed as follows with respect to roentgenographic changes: negative, nine; linear-nodular, eight; and nodular-confluent, nine. In all patients the minute ventilation was adequate, and the decreased exercise oxygen uptake on air breathing indicated the presence of increased pulmonary vascular resistance and thus the inability to expand the pulmonary vascular bed adequately. There was a lack of correlation between the exercise-oxygen uptake and the roentgenographic changes.

The degree of pulmonary function impairment was classified as normal, slight, moderate, or severe on the basis of the battery of tests described. In the group of 98 workers, 30 were classified as normal, 48 with a slight degree, 14 with a moderate degree, and only 6 with a severe degree of pulmonary function impairment (table 3). In the group with normal function, 16 had negative roentgenographic findings, 9 had linear-nodular changes, and 5 had nodular-confluent changes. In the group with a slight degree of function impairment the roentgenographic changes were classified as 20 negative, 18 linear-nodular, and 10 nodular-confluent. In the group with a moderate degree of functional im-

TABLE 3.—*Correlation Between Degree of Pulmonary-Function Impairment and Roentgenographic Classification in 98 Diatomite Workers*[10]

	Degree of Pulmonary Function Impairment†				
Roentgenographic Stage*	Normal	Slight	Moderate	Severe	Total
Negative	16	20	5	0	
Total cases negative					41
Linear-nodular					
1st stage	7	12	5	0	
2nd stage	1	2	0	0	
3rd stage	1	4	0	1	
Total linear-nodular cases	9	18	5	1	33
Nodular-confluent					
Nodular 2nd, confluent 1st	3	2	1	0	
Nodular 3rd, confluent 1st	0	2	0	0	
Nodular 2nd, confluent 2nd	2	3	1	3	
Nodular 3rd, confluent 2nd	0	3	2	2	
Total nodular-confluent cases	5	10	4	5	24
Total cases, all stages	30	48	14	6	98

* Roentgenographic classification of U. S. Public Health Service.[9]
† Over-all evaluation based on complete battery of tests as described, Motley.[5]

pairment five had negative findings, five presented linear-nodular, and four had nodular-confluent roentgenographic changes. In the six patients with a severe degree of functional impairment, one showed linear-nodular and five nodular-confluent roentgenographic changes. There was an over-all lack of correlation between the degree of pulmonary function impairment and the roentgenographic findings in the group of diatomite workers. Similar findings have already been reported for both hard-coal and soft-coal miners' pneumoconioses.[1]

In a previous report on 11 patients with diatomite pneumoconiosis who presented clinical symptoms of disability, the changes in function were typical of emphysema and fibrosis.[11] Heating of crude diatomaceous earth changes amorphous silicon dioxide to crystalline cristobalite, a silicosis-producing substance, and exposure to this dust resulted in marked pulmonary insufficiency in less than five years, in some cases, before dust control measures were instituted.[12]

Summary

Determination of the extent of the impairment of pulmonary function from inhalation of silica or other mineral dusts such as silicates, asbestos, carbon, smoke, coal, alumina abrasives, iron, or chalk requires pulmonary function measurements with adequate tests to evaluate (1) the ventilatory status, (2) the transport of oxygen and carbon dioxide in the lungs, and (3) the pulmonary blood flow. Single tests of lung function or tests of only one aspect are unsatisfactory. Roentgenographic changes constitute no reason to remove the worker from the job, as demonstrated in the 98 diatomite workers studied. No further progression may occur if dust control in the plant is improved. If serial follow-up studies of pulmonary function reveal significant progressive changes, then the worker should be removed before total disability occurs. There is great need for more extensive application of accurate pulmonary function testing in industry, which means that mere determination of timed vital capacity is inadequate.

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HEALTH IN RELATION TO CULTURE.—Some consider that culture is operating to man's biological detriment—specifically that medicine, by suspending the operation of the natural selection that would eliminate the physically defective, is endangering man's biological inheritance, and that this must be corrected by a program of artificial selection, of eugenics. My feeling is that we simply don't know enough about the operation of biological or cultural laws for intelligent decision; that whatever the biological consequences, we are caught in the stream of culture, and that we must try to operate with the currents of that stream. The problems are both urgent and fascinating. That their understanding will require the fusion of biological, medical and cultural points of view, certainly does nothing to detract from their fascination.—Medicine and Anthropology, New York Academy of Medicine, Lectures to the Laity, vol. 21, edited by I. Galdston, International Universities Press, Inc., 1959.

PLASMA LEVELS OF EPINEPHRINE AND NOREPINEPHRINE—ANESTHETIC SIGNIFICANCE

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Clues as to the causation and treatment of hypotension during general anesthesia were sought in a study of the concentration of catechol amines in the plasma. An initial blood sample was taken just before induction and a second sample about an hour after the induction of light surgical anesthesia. The concentrations of epinephrine and norepinephrine in the plasma were determined thus in 47 patients who received general anesthesia and in 9 who received spinal anesthesia. Because of the magnitude of the normal variations and the smallness of the groups, however, no statistically valid conclusions were possible. The data obtained in this study did not confirm the reports of earlier investigators. The rises in catechol amine levels with use of ether and halothane were only suggestive, and the data did not afford any basis or theories as to the hemodynamic effects of the anesthetics used.

Epinephrine and norepinephrine, collectively referred to as catechol amines, have a profound effect on the cardiovascular system when given parenterally or increased from endogenous sources such as the adrenal medulla. What role the catechol amines play in maintaining a physiological state under anesthesia is not clearly understood. The stimulating effect of these amines and the opposing direct myocardial depressant effect of anesthetics are well recognized. Certainly, if anesthetic agents could be shown to alter the amount of the endogenously produced catechol amines, the anesthesiologist would be in a better position to select one certain anesthetic agent in preference to another.

The changes in plasma catechol amine levels that occur in dogs have been determined for ether, chloroform, vinyl ether (Vinethene), and thiopental sodium. In plane III of surgical anesthesia, with use of the volatile anesthetic agents, these amine levels were increased four to six times, whereas thiopental sodium anesthesia did not produce a significant rise.[1] Associated with this increase in the catechol amine levels when ether, chloroform, or vinyl ether was used, there occurred, on emergence from anesthesia, changes in the heart's contractile force which were interpreted as being due to an increase in sympathoadrenal activity.

In human subjects, the administration of cyclo-pane has been shown to produce an insignificant crease in the plasma epinephrine concentration ut a significant rise in the concentration of norepinephrine[2]; the same findings have been recorded with ether anesthesia. Halothane (Fluothane) and thiopental sodium, however, were found to produce little change. It has been implied that this lack of increase in the plasma catechol amine levels with use of halothane and thiopental sodium could explain the hypotension that is often observed during anesthesia with these agents, whereas the lack of hypotension noticed with use of cyclopropane and ether could be accounted for by the rise in catechol amine levels.[3]

To relate these previously mentioned findings to the clinical practice of anesthesiology, the plasma catechol-amine levels were measured in a group of surgical patients who underwent a variety of elective procedures.

Method of Study

The four anesthetic agents chosen for investigation were cyclopropane, combined thiopental sodium and nitrous oxide, ether, and halothane. Spinal anesthesia was included for completeness. Cyclopropane was given by the closed-circle technique, and the other inhalation agents were administered by the semiclosed-circle technique. Spinal anesthesia was administered by both single injection and the continuous technique.

On arrival in the operating room, after the patient had received an appropriate preoperative dose of narcotic and a belladonna drug one hour previously, a control sample of blood was withdrawn. One hour later, during which time light surgical anesthesia was administered, another sample of blood was obtained.

A sleeping dose of intravenously given thiopental sodium preceded the administration of cyclopropane, ether, and halothane. After the administration of succinylcholine chloride for muscle relaxation, endotracheal intubation was performed in most patients. If muscle relaxation was required during the operation, a continuous drip infusion of succinylcholine was used.

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Read before the Section on Anesthesiology at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 12, 1959.

The blood specimens were assayed for the concentration of the plasma catechol amines, with use of the method of Weil-Malherbe and Bone as modified by Richardson and associates.[4]

The patient's anesthesia record and postoperative course were reviewed for any findings which might be correlated with changes in the plasma concentration of catechol amines.

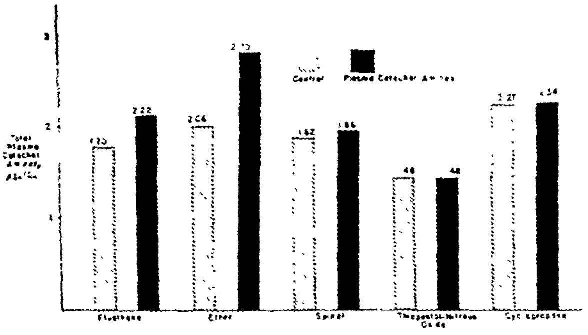
Table 1.—*Type of General Anesthetic or Agent Administered*

Agent or Type	No. of Patients
Halothane	12
Ether	12
Thiopental sodium-nitrous oxide	11
Cyclopropane	12
Spinal	9

Results

A total of 47 patients received general anesthesia, and the grouping of these patients according to the anesthetic agent administered is listed in table 1. Nine patients received spinal anesthesia. The age range was from 7 to 78 years, with a mean age of 47 years. The distribution between men and women was about equal, and the types of surgical procedures performed were varied, with no one particular operation more common than another.

The range of total plasma concentration of the catechol amines in the control specimens varied from 0.88 to 4.67 mcg. per liter, with an average concentration of 2.20 mcg. per liter, which is well within the normal range if the laboratory technique mentioned above is used. The largest increase in total plasma catechol amine levels that was observed at the end of one hour of anesthesia occurred with use of ether and next with use of halothane. Spinal, thiopental sodium-nitrous oxide, and cyclopropane anesthesia caused hardly any rise (see figure). The increase in plasma concentration of catechol amines with use of ether and halothane anesthesia is, however, not statistically significant.



Change in total plasma catechol amine levels after one hour of anesthesia.

Of interest are the changes which occurred in the epinephrine and norepinephrine fractions after one hour of anesthesia. Halothane and ether anesthesia produced a suggestive increase in the epinephrine fraction but little or no increase in the norepinephrine fraction (table 2). Spinal, thiopental sodium-nitrous oxide, and cyclopropane anesthesia did not produce any measurable change in either fraction.

Table 2.—*Mean Plasma Levels of Epinephrine and Norepinephrine After One Hour of Light Surgical Anesthesia**

Anesthesia, Agent or Type	Epinephrine, µg./Liter		Norepinephrine, µg./Liter	
	Control	Anesthesia	Control	Anesthesia
Halothane	0.27 (0.00-0.45)	0.52 (0.15-1.14)	1.42 (0.84-4.32)	1.70 (0.62-3.32)
Ether	0.32 (0.07-0.74)	0.72 (0.20-1.58)	1.74 (0.72-3.13)	1.98 (0.53-5.60)
Spinal	0.35 (0.15-0.68)	0.41 (0.19-1.10)	1.37 (0.79-1.92)	1.46 (0.62-1.90)
Thiopental sodium-nitrous oxide	0.34 (0.10-0.84)	0.35 (0.00-0.98)	1.05 (0.39-3.16)	1.16 (0.00-2.50)
Cyclopropane	0.49 (0.21-0.95)	0.50 (0.07-1.42)	1.78 (0.91-3.63)	1.83 (0.26-3.78)

*Figures in parenthesis represent range of concentrations.

Unsatisfactory Course of Anesthesia or Postanesthesia Recovery, or Both

Since the catechol amines have a profound influence on the cardiovascular system, the patient's course during anesthesia and immediately after anesthesia was reviewed for significant changes in blood pressure or pulse rate. Most patients responded to anesthesia in a clinically satisfactory manner. Hypotension of a significant degree occurred in eight patients. The most severe hypotension, however, occurred in the two patients who had received thiopental sodium-nitrous oxide anesthesia, and in one of these patients no catechol amines could be detected after one hour of anesthesia. Hypotension after spinal anesthesia was not considered an unsatisfactory response but rather an accompaniment of this technique.

Table 3.—*Total Plasma Catechol Amine Levels in Patients with Hypotension After One Hour of Anesthesia**

Anesthetic Agent	µg./Liter, Control	µg./Liter, One Hour After Anesthesia
Halothane	1.10	1.24
Ether	2.00	1.75
Thiopental sodium-nitrous oxide	0.77	0.41
Cyclopropane	3.37	2.57

*Two patients received each agent.

The average total plasma catechol amine levels in the eight patients who developed hypotension appear in table 3, and, except for halothane, the values listed are less than the control values.

Comment

Thiopental sodium-nitrous oxide,[5] alone or combined with spinal anesthesia,[6] has been recommended for patients with hyperthyroidism, on the clinical basis that these agents have little or no effect on the secretory activity of the adrenal medulla. The barbiturates have been shown to decrease the sensitivity of the adrenal medulla to chemical stimulants.[7] Any increase in adrenal medullary activity would place a further burden on an already damaged cardiovascular system. Certainly, the patients included in this study showed no significant increase in their total plasma catechol amine levels. Although cyclopropane produced no significant increase in the total plasma concentration of catechol amines, this agent might best be avoided in patients who already reflect an increase in sympathoadrenal activity.

What conclusions can be obtained from the decrease in plasma catechol amine levels that was observed in those patients who became hypotensive? The number of patients in the study is much too small to arrive at any significant conclusion; however, it is interesting to postulate that a contributory factor in these hypotensive patients may have been their inability to produce sufficient amounts of these amines to oppose the direct cardiac depressant effect of the anesthetic agents used. Halothane, on the other hand, is a powerful cardiac depressant,[8] and the slight rise in catechol amine levels may not have been enough to overcome this depressing effect.

The increases observed in the total catechol amine levels are not statistically significant; therefore, this report does not confirm the findings reported by the previously mentioned authors. This discrepancy may be the result of differences in the method of study, such as varying depth of anesthesia and the use of premedicant drugs and thiopental sodium for induction of anesthesia. Furthermore, age is recognized as a significant determining factor, since it has been shown that infants and children exhibit a greater tendency toward increased sympathoadrenal activity under anesthesia than adults.[9]

Summary

Changes in plasma catechol amine concentrations were investigated in 47 patients who received general anesthesia with halothane (Fluothane), ether, combined thiopental sodium and nitrous oxide, and cyclopropane. Nine patients received spinal anesthesia.

A statistically insignificant increase in the total plasma catechol amine levels after one hour of light surgical anesthesia was noted with use of halothane and ether. Cyclopropane, thiopental sodium-nitrous oxide, as well as spinal anesthesia produced little or no change in the total amine levels. There was a suggestive increase in the epinephrine fraction with use of ether and halothane as anesthetic agents.

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SENIOR SURGEONS.—Some senior surgeons seem to believe that among their attributes is the quality of bacteriologic sterility. These men tend to operate with their masks resting on their upper lips. They also come to the operating rooms to offer a cheery reassurance to their patients before anesthesia is started, entering the operating theatre in street clothing, without cap or mask. The hospital administration, the infection committee, or the executive committee of the department of surgery should take appropriate action to eliminate this problem.—J. Jacoby, M.D., C. R. MacPherson, M.D., C. Ziegler, M.D., and J. Garvin, M.D., The Anesthesiologist and Hospital Infections, *Anesthesia and Analgesia*, January-February, 1960.

PHLEBOGRAPHY OF THE LOWER EXTREMITY

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The method of deep-vein phlebography here described has been applied in 251 extremities of 159 patients over a period of two and one-half years. The results have often been decisive in planning treatment because of the importance of distinguishing between incompetence and thrombosis of the deep veins. The films to be exposed must be 86 cm. long and 36 cm. wide in order to show the desired portions of both legs simultaneously. The contrast medium is injected into a dorsal vein of the foot, and three carefully timed roentgenograms are made. Preliminary tests for sensitivity are necessary, and patients must be told to expect pain in the injected feet; other complications have been few. Correct interpretation of the phlebograms obtained depends on the diagnostician's awareness of the pitfalls here described, particularly in the diagnosis of thrombi.

Satisfactory contrast demonstration of the main deep veins of the leg has proved to be difficult. Poor mixture between blood and contrast substance resulting from the relatively slow-moving and voluminous venous pool must be overcome. A readily accessible injection site is required to reach as many as possible of the important deep veins. Dissipation of the opaque substance in the superficial venous system must be avoided since this system can be evaluated adequately by ordinary clinical methods. An upright posture and exercises are necessary if the functional capacity of the deep veins is to be assessed. Examination of the entire lower extremity requires films at least 34 in. long in an average adult patient. Finally, the interpretation of phlebograms can be confused by variations in the course and character of the veins. We sympathize with the clinician who is discouraged by any given method before its clinical value can be tested.

The method of deep vein phlebography discussed here is similar to that described by Shumacker, Moore, and Campbell,[1] and Bauer[2] and has been used fruitfully at the University of Rochester Medical Center in 251 extremities of 159 patients over a period of two and one-half years. It has proved practical and informative. Its acceptance has been encouraged by a continuing detailed study of its real value as an ancillary method in the diagnosis and clinical management of venous abnormalities. Although it has technical failings, increasing familiarity in both execution and interpretation has helped to keep these in proper perspective. As with any other time-consuming diagnostic procedure, a combination of interest, optimism, persistence, and experience were required to establish the usefulness of this technique of phlebography.

Clinical Uses

At first a detailed analysis was made of the accuracy and of the morphologic and functional data obtained by this method in 62 extremities.[3] On reasonably firm clinical grounds, these extremities were assumed to be either normal or postphlebitic or to exhibit only varicose veins. On the basis of the experience with this group another analysis was made of the clinical applications of this particular routine method of phlebography in studying selected clinical problems.[4]

Patients chosen by us for phlebography can be grouped into two general categories. The first group of patients are those suspected to be suffering from incompetency of the deep venous system. They have unexplained swelling or obvious venous stasis. With these patients the question arises of whether signs are due to deep vein abnormalities or merely to superficial varicosities and incompetent perforators. The second group are those suspected to have deep venous thrombosis. They lack sufficient clinical evidence of thrombosis to justify definitive therapy, or they have pulmonary infarction but no obvious source of emboli. In addition, patients who show clear-cut clinical evidence of deep venous thrombosis may also be studied in order to provide a basis for evaluating the anatomic and functional results from various forms of surgical or medical therapy.

We feel that any reasonably accurate method of judging the anatomic and functional status of the deep veins of the leg in such patients can have important implications in guiding rational therapy.

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Read before the Section on Radiology at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 11, 1959.

Method

1. Sensitivity testing is performed by intravenous or intradermal injection of the contrast medium. The patient is reassured and coached in the details of the procedure.

2. Percutaneous puncture or cut-down is made into any vein on the dorsum of the foot with a short 18-gauge or 20-gauge needle. Infusion of isotonic sodium chloride solution is begun through a three-way stopcock.

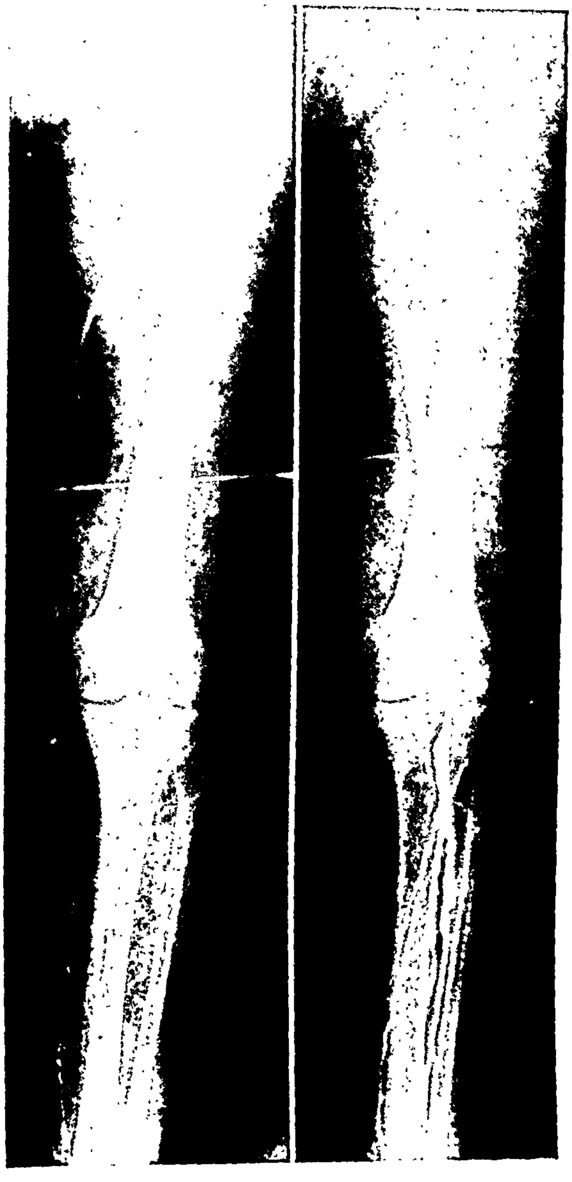

Fig. 1.—*Left*, failure to fill deep veins by deliberate omission of tourniquet. Only greater saphenous system is filled. *Right*, second injection is made into same foot vein immediately, but with tourniquet at the ankle. Deep veins are well filled at all levels. Narrowing of popliteal vein behind knee joint space is from extrinsic pressure of hematoma in popliteal space. Examination ruled out deep phlebothrombosis as possible cause for swelling.

3. The patient is placed in a semi-erect posture, 60 degrees up from the horizontal, with his feet on a small stool which rests on the footboard of the table.

4. A tightly occluding tourniquet is placed above the ankle.

5. Forty cubic centimeters of a 50% diatrizoate (Hypaque) sodium solution are injected slowly over a period of one minute into each extremity being examined. Both sides are frequently examined simultaneously.

6. At the end of injection, the first radiograph of the entire leg is made. A 14-by-36-in. spring cocking Potter-Bucky diaphragm is permanently mounted under the top of our tilting table. The 14-by-36-in. cassettes with intensifying screens can be loaded with 14-by-36-in. film or, as we now prefer, with two 14-by-17-in. films butted together accurately inside each cassette. A distance of about 56 in. between the film and the tube is required to expose this large area. There is a wedge filter at the tube window for equalizing radiographic density from calf to thigh and also a rectangular lead diaphragm which acts as a primary cone. The field is coned to a full 14-by-36-in. so that both extremities can be examined simultaneously. General features of this equipment are illustrated elsewhere.[5]

7. The tourniquet is removed, and the patient is instructed to pump up and down on the balls of his feet 10 times.

8. A second long radiograph is exposed. This will be about 30 or 40 seconds after the first.

9. In most cases, the cassette tray and x-ray tube are then shifted as rapidly as possible to make a third 14-by-17-in. radiograph of the pelvic region. Our hope to visualize the iliac veins in this way proved possible in many of our patients.

10. After the third radiograph has been made, the patient is placed in a horizontal position, and the infusion of isotonic sodium chloride solution is flushed rapidly through the needle to clear the opaque substance from the veins.

11. Ten minutes later, a single abdominal radiograph provides an excretory urogram. We attempt to obtain this additional examination in most of our angiographic procedures.

The patient must be in an upright position for satisfactory mixing of the opaque substance with blood, for good demonstration of valve cusps, and for persistence of satisfactory contrast during the period of filming.[6] Having the patient in this position also helps to simulate the principal physiological problem in the venous circulation of the leg, which is to overcome the effect of gravity. The use of any foot vein and of the tourniquet is the simplest method for assuring anterograde filling of the deep veins without excessive filling of the superficial network[7] (fig. 1). The experience of Felder and Murphy[8] guided us in the routine use of a somewhat larger bolus of contrast substance than previously suggested in the literature, particularly since our purpose was to study the entire deep venous system of the leg, by one injection when possible.

The vigorous standard exercise helps to mix the contrast medium, redistribute it in the veins, and propel it cephalad. The occurrence of poor propulsion or poor peripheral emptying corroborates the diagnosis of venous stasis. Streaming or mixing artifacts tend to disappear on the postexercise radiograph, which frequently has relieved doubt about the integrity of a vein or its valves. Some deep veins not yet filled on the first radiograph, particularly the thigh veins, will be clearly identified on the second[6a] (fig. 2). Importance of a lack of filling or defect in a vein can be corroborated by persistence on the second exposure. Opaque substance may appear or increase in the superficial system after exercise, which makes possible a partial study of incompetent perforators in the calf and thigh.

Problems and Complications of Method

Since we have used the 14-by-36 in. Potter-Bucky tray and cassettes for many years in arteriographic and orthopedic procedures, there was no problem in availability of equipment for long filming. Cassette changing in the Potter-Bucky tray is easy in serial phlebography performed on a patient in a semi-erect position because there is no great pressure of speed as there is in serial arteriography. Protection of personnel is accomplished simply by permitting them to retreat before any exposure is made. Unquestionably, stereoscopic or lateral filming would add something to the accuracy of our anatomic interpretation. Yet we have decided deliberately to forego any possible advantages from these additional steps in procedure so that the routine can be kept to a feasible and uncomplicated minimum.

Only rarely has cut-down been required to find a foot vein, usually in a very edematous extremity. Although the foot veins tend to be elusive during percutaneous puncture, we have made successful venipuncture for phlebograms with gratifying regularity. The complications from injection of a 50% diatrizoate sodium solution in large volume have been very few. Only a few patients have fainted during the two or three minutes necessary for radiography of patients in an upright position.

The incidence of urticaria, flushing, or vomiting have been no greater than we encounter during ordinary antecubital injection of smaller volumes of a 50% diatrizoate sodium solution during excretory urography. In 92 of our 159 patients both legs were examined simultaneously, which required 80 cc. of the contrast medium. On several occasions, we decided after inspection of the first set of roentgenograms to make an immediate repeat injection into one or both extremities, which raised the total volume for the procedure to 120 or 160 cc. One of our patients was examined with 120 cc. of this substance one day and with another 120 cc. two days later without untoward reaction.

However, pain in the foot has been experienced by most of our patients during injection, and many also have had pain in the calf. These symptoms disappear promptly on the patient's return to horizontal position and on infusion of isotonic sodium chloride. We are careful to warn the patient of this.

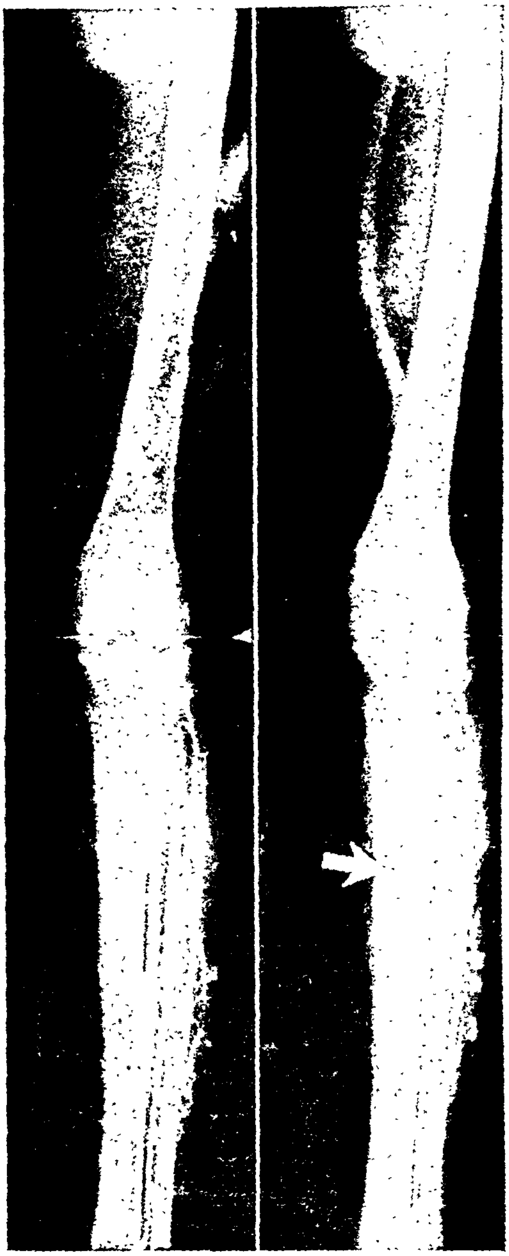

Fig. 2.—Complicated varicose vein problem. *Left,* before exercise, deep veins of the calf are filling well, except for posterior tibial vein. Popliteal vein is shown only up to knee joint, and there is no filling of "superficial" femoral vein in thigh. *Right,* after exercise, calf veins do not empty well. Now posterior tibial vein has filled (*arrow*) as well as entire "superficial" femoral vein. There is relative paucity of valves and slight general dilatation. Extremity reveals the type A abnormal deep venous system.

Pain is most severe and prolonged when the main deep veins have been shown to be partly or completely blocked, as in patients who are postphlebitic or who have acute massive phlebothrombosis.

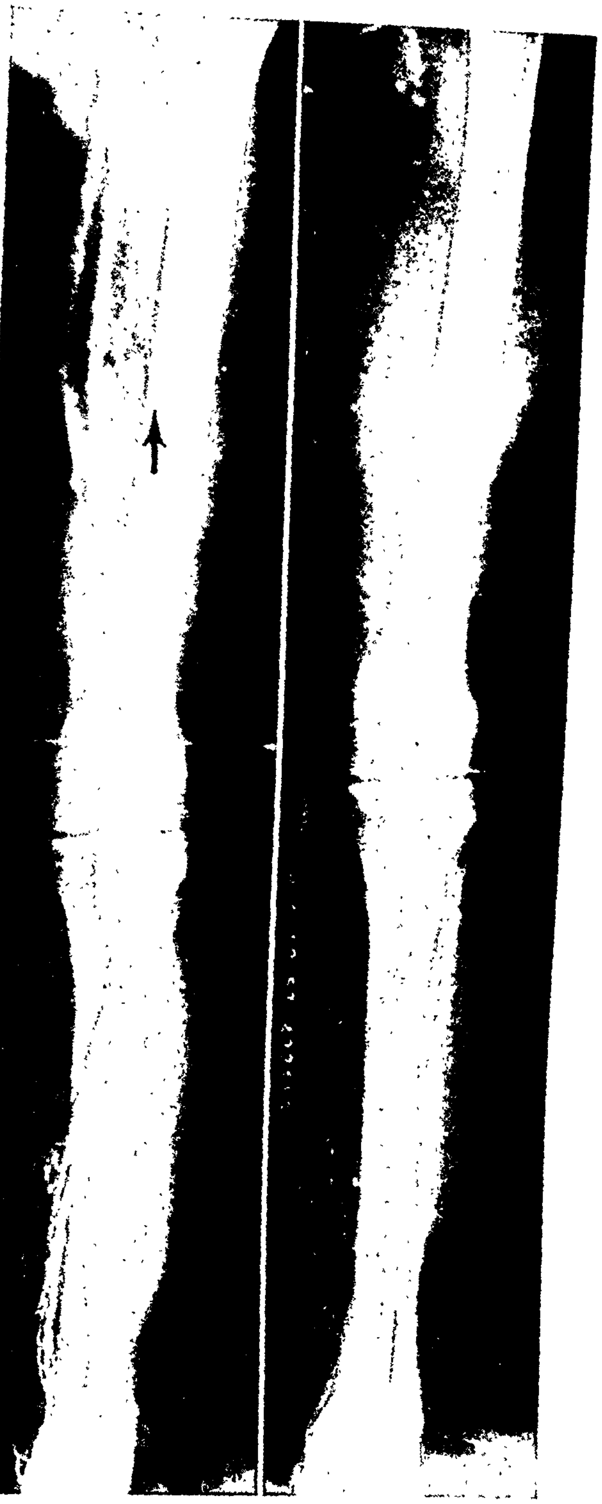

Fig. 3.—Normal patient (*left*) before exercise and (*right*) after exercise. The "deep" femoral vein fills through distal connection with popliteal vein (*arrow*). Double "superficial" femoral vein is a common variant. Normal valve cusps will retain opaque substance after exercise.

Nevertheless, we have not been able to recognize any incident of deep vein thrombosis after the procedure, nor do we feel that the course of a known phlebothrombosis has been altered recognizably by it. We believe that it is important to stress the satisfactorily benign nature of this type of phlebography in a carefully evaluated and followed group of patients, even in those with acute phlebothrombosis. Our empirical conclusions are based at this writing on 159 patients in whom there have been 273 injections of one or both extremities. Only two patients have developed local acute superficial phlebitis at the injection site. Extravasation has occurred occasionally and has not proved serious except in one patient. In this patient, a tissue slough occurred when skin grafting of a neighboring varicose ulcer was attempted a short time after the extravasation.

There have been no proved cases of pulmonary embolism or infarction after the procedure. One patient is said to have coughed blood on the morning after examination, but a diagnosis was not established. In obvious cases of acute phlebothrombosis we restrict the amount of exercise during the examination.

Phlebographic Anatomy and Pathology

Normal Extremities.—Normal deep thigh veins have smooth parallel walls and sharply demonstrated valve cusps. In the calf, the anterior tibial, peroneal, and posterior tibial veins taper slightly and are often and unpredictably doubled. They usually have numerous valves. The popliteal vein has a varying point of division in relation to the knee joint and only one or two valves. The "superficial" femoral vein is doubled over a varying distance in about 28% of normal extremities and has from one to six valves. (Since both the superficial and the deep femoral veins are in the deep system, we use quotation marks to avoid confusion.) In about half of our patients the "deep" femoral vein is well demonstrated because it has a distal connection with the popliteal vein and receives the opaque substance directly as it ascends in the extremity (fig. 3). In most other cases, in which there is no distal connection, the "deep" femoral vein is seen only partly at its upper end or not at all, depending on reflux from the common femoral vein or connections with the partly opacified superficial network.

Having identified the main deep veins, we arbitrarily assign the term "accessory veins" to all others noted on the radiograph. Without stereoscopic or lateral views accurate identification is impossible. Some of these accessory veins are superficial, some are deep collaterals and tributaries, and some are perforators. Accessory veins with predominantly horizontal orientation we term "communicators"; some of these are perforators. Accessory veins oriented vertically we call "collaterals." The normal extremity demonstrates few or no accessory veins by this method. After exercise, emptying of both deep and accessory channels tends to be good or excellent. Valve cusps may remain in clear relief however (fig. 3).

Venous Stasis of the Extremities.—The extremities may have abnormal deep veins which tend to be of two varieties:

Type A: Some patients with varicose veins may demonstrate deep channels which are wider than normal and lack valves but have smooth walls and no filling defects (fig. 2). These changes are presumed to be due either to congenital variation or to degenerative processes, but they are seen in only one-third of the patients with varicose veins. The remainder of the patients appear to have normal deep veins.

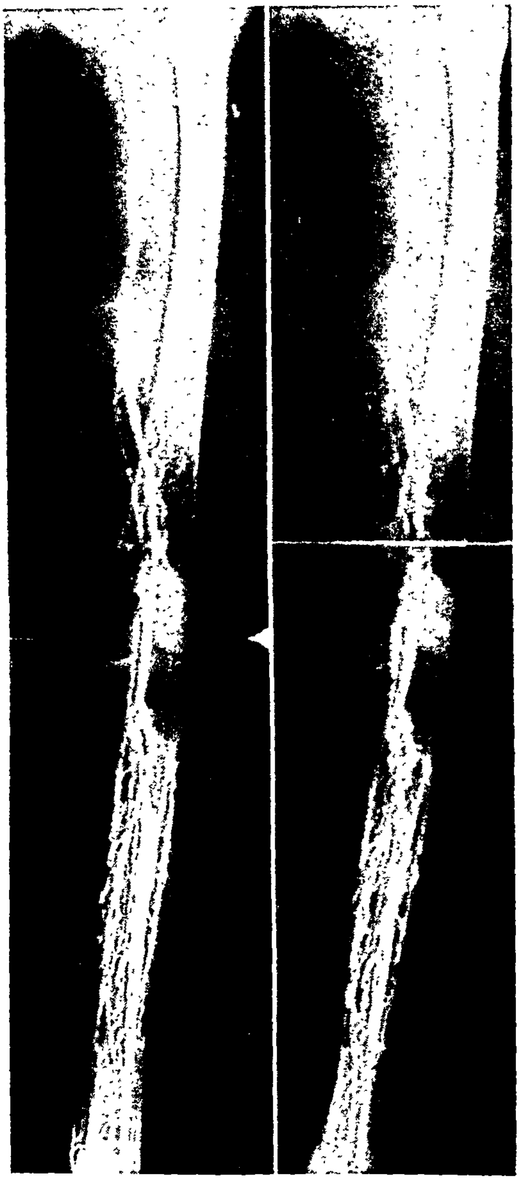

Fig. 4.—Venous stasis problem in patient who probably had iliofemoral thrombosis and has "type B" abnormal deep veins at all levels.

Type B: Patients with clear histories of previous deep phlebitis may demonstrate patent deep veins, but these are characterized by lack of valves and irregular walls and channels and have never in our experience been wider than in normal patients (fig. 4).[9] Some of the patent deep veins in postphlebitic extremities are only collateral bypasses[10] or venae comitantes,[9] but many are actually recanalized main veins.[11]

The patients with varicose extremities generally demonstrate more accessory veins than normal patients by our technique, and postphlebitic patients generally reveal the greatest number of these communicators and collaterals. When the deep thigh veins can be called abnormal in the sense of either type A or type B there is only fair or poor emptying after exercise and the accessory veins fill or increase rather than empty.[3]

Extremities with Acute Phlebothrombosis.—In patients with acute phlebothrombosis, deep veins which contain fresh clots may be absent on the radiographs, or the opacified vessel will demonstrate characteristic defects (fig. 5). Such defects are defined in the next section.

Possible Pitfalls of Method

Identification of Calf Veins.—Identification of the calf veins may be difficult with single anteroposterior radiographs. The three main veins overlap and join at varying levels to form the popliteal vein and are varyingly paired or doubled. The cortex of the tibia and fibula will hide valvular detail or filling defects on occasions. Superficial veins can be particularly confusing. The lesser saphenous vein imitates the course of the peroneal vein and can be mistaken for it. When numerous deep and superficial accessory veins are filled, as in certain postphlebitic or varicose extremities, particular care is necessary to avoid being distracted by the profusion of small vessels. We have recognized that stereoscopic and lateral radiographs would help to overcome such confusion, but we have avoided encumbering the procedure with additional maneuvers required to obtain them.

Failure to Fill Calf Veins.—Since lack of filling of a deep calf vein may represent nothing more than a failure of the method in a significant percentage of patients,[3] it cannot alone be taken as unequivocal evidence of thrombosis. On one occasion, filling of the deep calf veins was unaccountably improved during a repeat examination by omitting the use of the tourniquet. This can be particularly true in the case of the anterior tibial vein, since this deep vessel is most likely to be occluded near the ankle by application of the tourniquet (fig. 6). In our study, complete filling of the anterior tibial vein was least satisfactorily recorded,[3] and we learned promptly to recognize this pitfall.

Inadequate Filling of Thigh Veins.—In patients with venous stasis, associated either with varicose veins or the postphlebitic state, there may be much dilution and pooling of contrast substance in the foot and calf. Even after exercise, the "superficial" femoral vein may not receive enough opacified blood to allow a critical study of its lumen and valves. The iliac veins also are not dependably filled in such cases. Therefore, on occasion we have had to resort to a second study by percutaneous injection into the common femoral vein in order to obtain crucial details about the upper part of the vein (fig. 7).

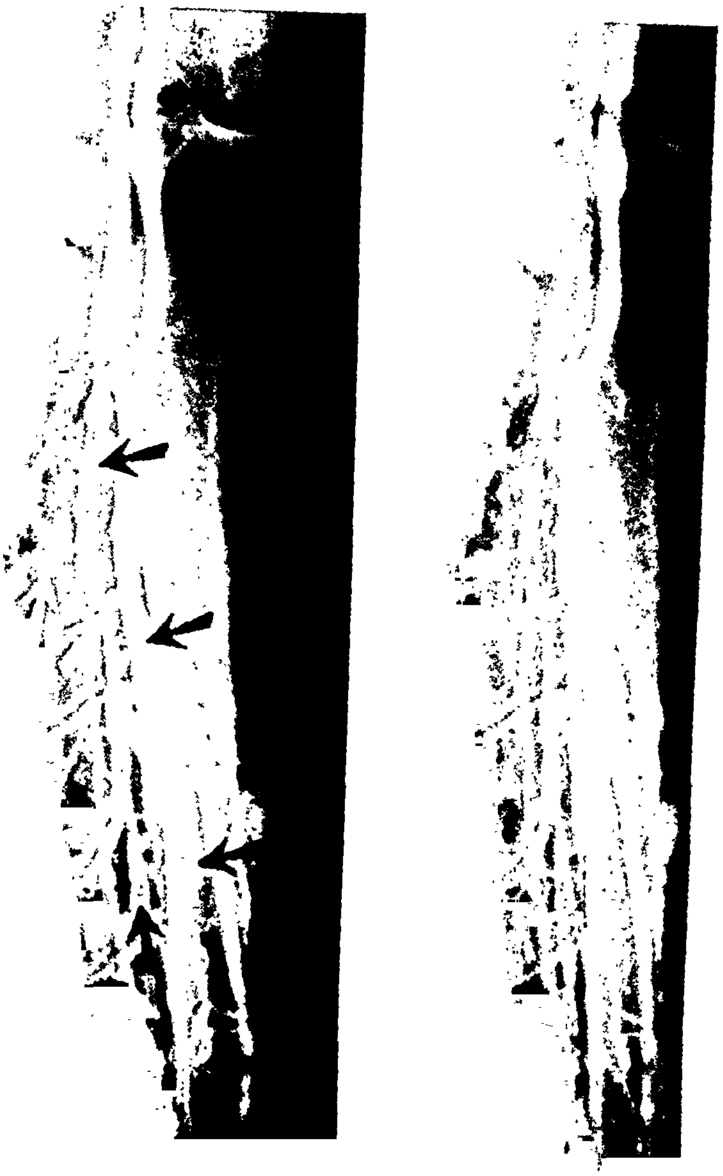

Fig. 5.—Acute phlebothrombosis involving several deep veins of calf in patient who had clinical onset two days after gastrectomy. Phlebogram was made seven days after first symptoms. Clot defects are noted in anterior tibial and peroneal veins (*black arrows*), but paired posterior tibial veins remain normal. There are also clots in communicator and perforator (*white arrows*). Small paired veins running horizontally or obliquely across lower fibula are characteristic perforators, which appear competent both before (*left*) and after (*right*) exercise.

It must be remembered that the "deep" femoral vein will be filled by this anterograde method in only half of the extremities, since only half will have the peripheral connection between it and the popliteal vein which will permit its receiving opacified blood from the peripheral injection site.

Equivocal Diagnosis of Deep Venous Thrombosis.—In view of possible streaming artifacts, always a plague to phlebographers, critical caution is recommended in identifying ragged vein margins as evidence of old thrombosis with recanalization or in concluding that small filling defects may be clots. It is fair to say, however, that such artifacts have proved to be a problem mostly in evaluating the "superficial" femoral vein, since dilution produces artifacts principally at the higher levels in our technique. As suggested above, retrograde phlebography by common femoral injection can help to clarify the status of the "superficial" femoral vein when this information is crucial, as in medicolegal problems. Catheterization of the lesser saphenous vein may provide a route for accurate filling of the "superficial" femoral vein, as discussed elsewhere by one of us.[9]

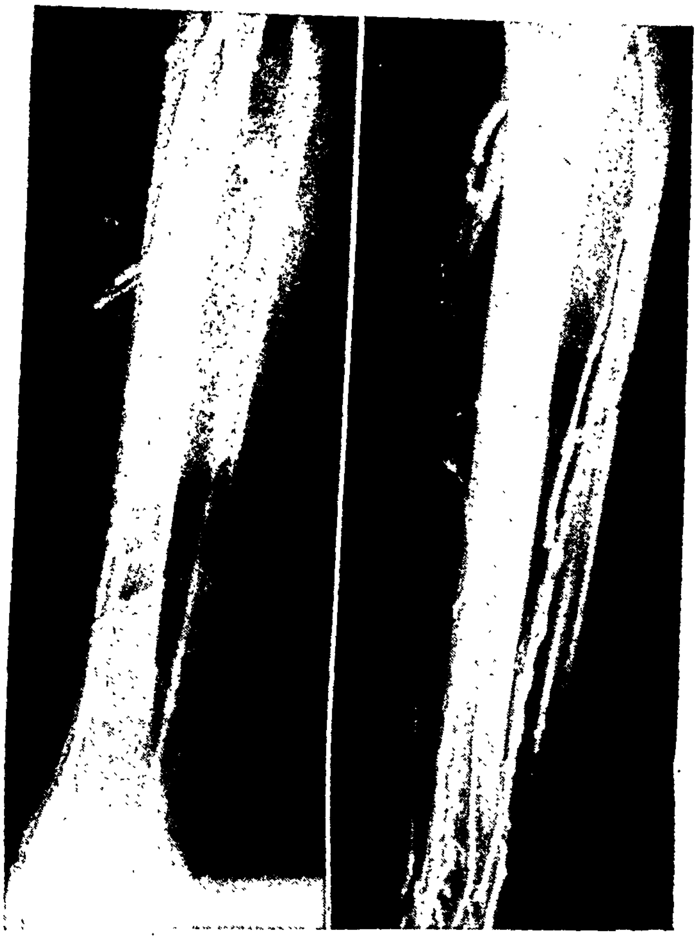

Fig. 6.—Tourniquet preventing adequate filling of anterior tibial vein. *Left*, routine foot vein injection has been made with tourniquet above ankle. Only paired posterior tibial vein fills well, and it appears normal. Segment of anterior tibial vein is seen high over fibula, with normal valve cusps. Peroneal vein was not visualized even after exercise. *Right*, second injection has been made. Because tourniquet was not used, both elements of paired anterior tibial vein are seen clearly to be normal. Portion of greater saphenous system, and some sural veins, are also filled. However, peroneal vein still is not seen.

In identifying clots in cases of questionable acute deep phlebothrombosis, we believe that any filling defect which has the following characteristics can be accepted as a thrombus: the defect must have sharp margins in an otherwise heavily opacified vein, and it must be seen identically on at least two radiographs (fig. 8). A filling defect which cannot pass such inspection remains as only a questionable clot.

Failure of any of the deep calf veins to fill may be assumed to be the result of thrombosis when the other deep veins show evidence of recanalization or characteristic collateral venous bypasses. When the characteristic filling defect of a clot can be identified at the upper or lower limit of an unfilled venous segment, we feel that the lack of filling may reasonably be ascribed to thrombosis. These features can establish with reasonable certainty that the patient is postphlebitic or in the course of thrombosis. If these criteria are not met, then failure to fill a calf vein is considered, at most, only equivocal evidence of thrombosis.

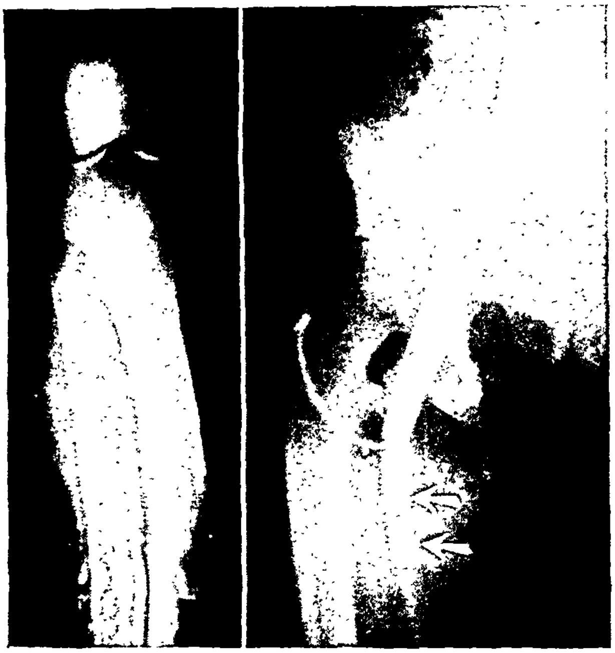

Fig. 7.—Failure to fill veins at higher levels by routine method. This patient had complicated varicose vein problem and venous stasis after tibial fracture 37 years previously. *Left,* even on postexercise radiograph, contrast medium has risen only into the middle of lower leg because of pooling in voluminous deep and accessory veins near injection site. However, deep calf veins do show normal valves and normally smooth walls where filled. *Right,* injection into common femoral vein demonstrates smooth walls and two valves (*arrows*) in the "superficial" femoral vein. Common femoral and iliac veins are also normal. There is no evidence of old phlebothrombosis.

Incomplete Identification of Incompetent Perforators.—This method of phlebography can help to answer questions concerning the integrity of the deep venous system. It may even show an incompetent saphenofemoral junction quite effectively. However, it is not recommended as a definitive method for demonstrating incompetent perforators to the satisfaction of the surgeon. It is true that many such incompetent perforators can be recognized, particularly on the postexercise radiograph, but there is apt to be too much dilution to permit any assumption that they are all being revealed. When identification of a particular suspected perforator is desired, therefore, a limited supplementary phlebogram can be obtained by injection locally into a neighboring superficial varix.

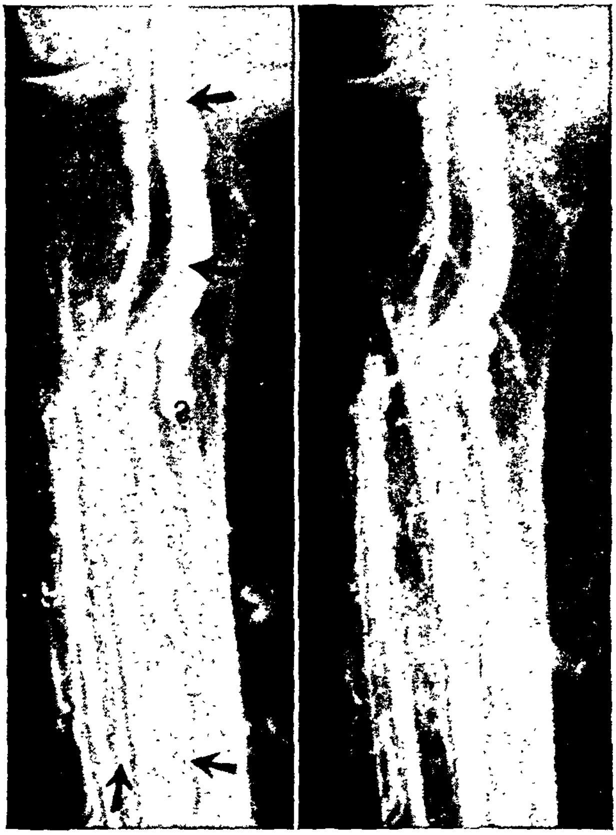

Fig. 8.—Acute phlebothrombosis in deep veins of calf and popliteal vein three days after clinical onset, which occurred six days after gastrectomy. *Left,* before exercise, clot defect is seen in popliteal vein (*upper arrows*) and in both elements of paired peroneal vein (*lower arrows*). (?) indicates a less characteristic segment of poor filling in posterior tibial vein which is probably also indicative of thrombosis in this particular phlebogram. The more strongly characteristic clot in popliteal vein, is shown on both pre-exercise and post-exercise (*right*) roentgenograms.

Summary

The method of long-film functional ascending phlebography discussed here demonstrates the main deep veins of the entire leg by one injection. Principal features of the technique are semierect position of the patient; application of a tourniquet above the ankle; and percutaneous injection of 40 cc. of a 50% diatrizoate (Hypaque) sodium solution into any vein on the dorsum of the foot. A 14-by-34 in. radiograph is made both before and after a vigorous standard exercise.

Complications have been minimal in the total group of 159 patients who have had 273 injections in single extremities. In 92 of these patients, both extremities were examined simultaneously on one or more occasions. No accident of deep vein thrombosis has been encountered, nor has the course of a known phlebothrombosis been altered recognizably as a result of the procedure.

By an evaluation of 62 extremities which were either normal, postphlebitic, or contained varicose veins the diagnostic accuracy of the technique has previously been established as satisfactory. We continue to use it as a routine method for demonstrating the deep veins in selected patients with questionable or obvious deep phlebothrombosis and in patients with venous stasis if there is doubt about the integrity of the deep venous system of the leg. Any such dependable method for testing the anatomic and functional status of the deep leg veins eventually should be applicable to therapy of extremities with similar venous problems.

We have learned to accept the pitfalls of method and interpretation that are unavoidable companions to any routine method of phlebography. Firm conviction of the clinical need for an accurate method has encouraged us to persist in its use and to urge its adoption by others who are similarly interested in venous disorders of the lower extremity. However, a combination of interest, optimism, persistence, and experience are required in order to recognize the true usefulness of this technique of phlebography.

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ANTITHYROID ACTIVITY OF THE TURNIP FAMILY.—Previous studies have shown that certain foods, especially rutabaga and turnip, possess antithyroid activity in man. The active antithyroid principle of the turnip family, goitrin, is released from a precursor, progoitrin, by enzymatic action. Earlier studies had indicated that cooking foods containing progoitrin would destroy myrosin, the specific hydrolytic enzyme which liberates goitrin from progoitrin. Therefore the cooked foods would have no antithyroid activity when eaten. Studies were made with crystalline progoitrin in man and the laboratory rat employing inhibition of radioiodine uptake as an index of antithyroid activity. Contrary to expectations, it was found that progoitrin would produce consistent antithyroid activity either with or without simultaneous administration of myrosin. It was possible to identify the appearance of goitrin in the blood and urine by spectrophotometric analysis and to determine that the yield of goitrin from progoitrin was quantitative. This indicated that hydrolysis of progoitrin occurs within the body in the absence of exogenous myrosin. This demonstration of antithyroid activity following the administration of pure progoitrin suggests that our concept regarding the innocuousness of cooked crucifers in the production of simple goiter should be revised. Progoitrin administered in a single daily dose of 1 Gm. was found an effective agent in the treatment of thyrotoxicosis in one patient.—M. A. Greer and J. M. Deeney, Antithyroid Activity Elicited by the Ingestion of Pure Progoitrin, a Naturally Occurring Thioglycoside of the Turnip Family, *The Journal of Clinical Investigation*, September, 1959.

MANAGEMENT OF DIFFUSE METASTASIS FROM CARCINOMA OF THE PROSTATE

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and
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Testosterone was administered to five patients suffering from metastases in carcinoma of the prostate. In each case the patient had diffuse metastatic lesions in bones and was no longer responding to estrogens, castration, or steroids. The testosterone was given in an attempt to stimulate bone and tumor metabolism and also to enhance the uptake of radioactive phosphorus for a therapeutic effect. The results are exemplified in the case of a man, aged 59 years, with bony metastases that had resulted in multiple fractures of ribs and vertebrae. After five days of treatment with testosterone, he received 2 mc. of radioactive phosphorus (P^{32}) every other day to a total of 20 mc. The beneficial effects were striking though temporary; it was not until the fourth month than any pain returned.

Early in the production of artificial radioisotopes the omnipresent element—phosphorus—was considered in its radioactive state for therapeutic application. The interest was deserved, because of its presence in nucleoprotein. From 1935 to 1940 Lawrence and Tobias [1] reported interest in radioactive phosphorus (P^{32}) in the treatment of cancer of the breast and prostate, but they abandoned research on the element when it became evident that differential absorption between the tumor and normal tissue was insufficient to produce known radiation dosages required for cancericidal effects. Holmes and Mee [2] studied the incorporation of radioactive phosphorus in nucleoprotein and demonstrated uptake in deoxyribonucleic acid synthesis.

In normal tissue lymphocytes, the granulocytic series and thrombocytes were found to be most sensitive to administration of P^{32}, followed by the gonads and intestinal mucosa.[3] Forssberg [4] reported that in his cases liver, spleen, and kidney had the same uptake of P^{32} as tumor tissue. Thus, the therapeutic result must be balanced against radiation damage in normal tissues by virtue of similar uptake or relative sensitivity to irradiation. Therapeutic interest led to trials in multiple myeloma and cancer of the prostate, with some reported benefit, but a long list of failures was also tabulated by many authors: retroperitoneal sarcomas, mycosis fungoides, carcinoma of the breast, seminoma, granulocytic and lymphatic leukemia, cancer of the gallbladder, osteogenic sarcoma, malignant melanoma, lymphoepithelioma, and angiosarcoma, to state but a few.[5] The outstanding trial was in patients with polycythemia vera, in which P^{32} became readily established as the preferred therapeutic agent. Consideration of the list indicates that benefits were directly related to the known sensitivity to radiation of the offending tumor cell, and there was no specific affinity for phosphorus beyond purely metabolic requirements in any tumor tissue. Studies reported in 1950 by Hertz [6] suggested concentration in many tissues of two to two and one-half times that calculated by homogenous distribution figures. Kenney's [5d] calculations indicated a yield of about 1,000 rads. Thus, only where such a low radiation dose was effective would any results be obtained and this at the sacrifice of adverse effects on certain normal tissues.

The alleviation of bone pain in metastatic breast cancer noted above was studied.[7] Radioautographs indicated marked concentration of the activity in areas of new bone formation compared with surrounding normal bone, soft tissues, and tumor cells. This has been confirmed by many persons. Since adult bone participates poorly in the pool of available P^{32}, compared with active tissue such as bone marrow constituent, it is evident that the finding of new bone formation in tumor-bearing areas would suggest a favorable situation for radiation of the adjacent tumor. Roentgenograms of osteoblastic metastases, excessive calcium metabolism, and alkaline phosphatase elevation seen in bone involvement of some cancers suggest some increased new bone formation. Finally, Albright's and Reifenstein's [8] contribution to the knowledge of bone metabolism suggests approaches to increasing bone formation with androgens and estrogens. In 1950 Hertz,[6] with such hormonal administrations, reported enrichment of the uptake 15 to 20 times above homogeneous distribution expectations. On a clinical basis, the Maxfields [7] reported palliation in a patient with metastases to the bone from cancer of the breast with use of radioactive phosphorus after enhancement with testosterone. Subsequent studies [9] were extended to patients with prostatic cancer and many other small series of cases have been studied.

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Present Study

The object of this report is to add to the number of cases of cancer of the prostate diffusely metastatic to bone, no longer affected by estrogen, castration, or steroid therapy, in which testosterone was given in an attempt to stimulate bone and tumor metabolism and enhance the uptake of radioactive phosphorus for a therapeutic effect.

Five patients (see table) with cancer of the prostate, all previously extensively treated with estrogens, castration, corticosteroids, and now resistant, were available for study. The medication schedule paralleled that generally used. In one patient (case 3) such marked exacerbation of pain occurred when taking testosterone that only a modest dose of P^{32} could be given before abandonment was required to avoid complete patient revolt. Interestingly, massive doses of estrogen and corticosteroids again relieved the pain. In the other four patients there seemed to be no great stimulation of the tumor or relief of pain from the testosterone alone. Subjective improvement occurred only with the administration of P^{32}, or thereafter. Relief of painful symptoms of metastatic prostatic cancer with testosterone has been recorded by Munger [10] but was not observed in this small group of patients. Of the last two patients, the fourth (case 4) had a marked reduction in the narcotic requirements for control of pain but subsequently died after operation; and the fifth (case 5) had a short remission of pain and no complications with the treatment. The second patient (case 2) had excellent remission of pain and decrease in narcotic requirements but, due to extenuating circumstances, was not available for further therapy and died six months after treatment from progression of disease. His terminal phase, however, was not complicated by pain or extensive narcotic intake.

Length of Control of Pain in Patients with Cancer of Prostate After Various Procedures

Case No.	Estrogen, Mo.	Orchiectomy, Mo.	Narcotics, Mo.	P^{32}, Mc., Dose	Course, Mo.	Survival Status, Mo.
1	7	3	No control	20	Local x-ray, 4½	Alive active, 11
2	24	24	2	10	Increasing narcotics, 3	Died
3	4	1	3	8	No control, pain exacerbated by testosterone	Terminal, 10
4	±* 12	12	2†	16	Controlled with narcotics, small amounts	Died, 2
5	±* 18	2	No control	10	Narcotics: increasing amounts, 3	Terminal, 8

* Equivocal response.
† No control after performance of cordotomy.

The first patient (case 1) was 59 years of age when his back pain was found to be due to metastatic cancer of the prostate, 15 months prior to this study. Estrogen administration controlled symptoms for seven months. Within three months he was bedfast but then obtained good remission for about four months after orchiectomy was performed. When admitted to the study, he was cachectic and bedfast; there were multiple pathological rib fractures and compression of several vertebrae. There were matted, fixed nodes in the left groin. His hemoglobin level was 6.2 Gm. per 100 cc.; reticulocytes 2.3%; abundant platelets; fibrinolysin, negative; serum acid phosphatase level 49 (King-Armstrong units, normal 0.3-4.5); and alkaline phosphatase level 62.6 (King-Armstrong units, normal 0-12). He required massive doses of narcotics for relief of pain. Two units of blood increased the hemoglobin level to 9.5 Gm. per 100 cc. After administration of 100 mg. of aqueous suspension of testosterone microcrystals for five days, a program was begun in which 2 mc. of P^{32} was administered intravenously every other day. A total of 20 mc. was given. Administration of testosterone was continued throughout treatment and for a week thereafter. On the last day of P^{32} administration a drill biopsy from the left ilium at the site of metastasis registered 500 counts per minute by Geiger survey meter. Assays by one of us (J. O. A.) showed 1.3 μc of P^{32} per gram of tumor and bone, a differential absorption ratio of 3 to 4, and an estimated irradiation dose of 1,000 rads.

At the end of one month the patient walked into the outpatient clinic; he had gained 12 lb. (5.4 kg.) and required no narcotic therapy. Results of his hematological studies will be presented later. During the next two months there was a total of 30 lb. (13.6 kg.) gain in weight and it was not until the fourth month that any pain returned, this being in the left thigh. Testosterone therapy was reinstituted and 10 mc. of P^{32} in 2 mc. aliquots was administered intravenously every other day, with complete relief of pain for two and one-half months. Then local left sacroiliac pain occurred but was relieved with local irradiation.

His hematological course is interesting and is presented in fig. 1. The expected fall in total leukocyte count followed by thrombocyte and erythrocyte depression after 5 mc. of P^{32} was administered in one week occurred in this patient. Recovery of normal hematological values was complete, even though with the amount of P^{32} administered one would have expected a prolonged depression. In fact, with the second administration of radioactivity there was practically no depression in the hemoglobin measurements. It is postulated that with so much tumor and osteoid tissue available to take up the radioactive phosphorus, the marrow was spared and consequently only a mild depression was seen.

When the roentgenogram of the pelvis at the beginning of treatment is compared with that two months after the second course of treatment with P^{32}, marked increase in calcification with healing of the osteolytic areas is seen (*fig. 2, left and right*). Fig. 3, *left and right*, demonstrates a radioautograph and histological section, with the activated emulsion corresponding to the sites of osteoid tissue rather than the aggregations of tumor cells.

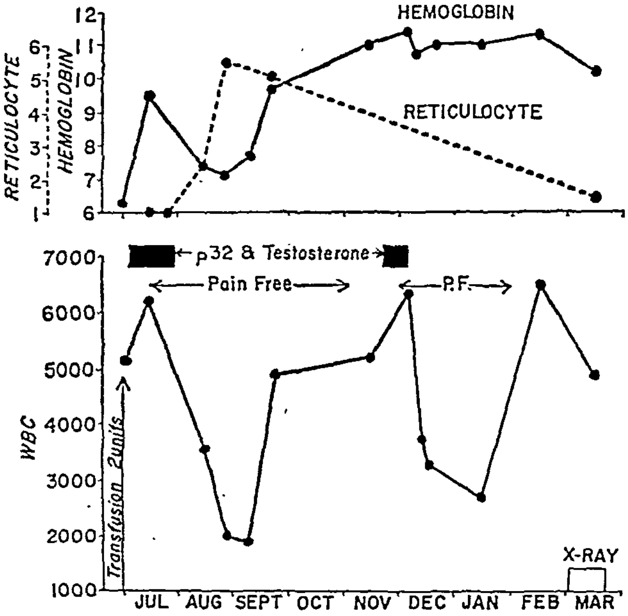

Fig. 1.—Composite plot of hematological response to administration of P^{32} and testosterone.

Comment

Here the questions of the inquirer and the doubts of the skeptic must end simple reporting. The most striking observation to be made must be that, although P^{32} was originally considered because of its position in nucleoprotein synthesis, its actual usefulness in the present situation seems to be due to its incorporation in bone salts (fig. 3, *left*). With accumulations of P^{32} in bone the lack of expected marrow depression by the radiation emitted may give a clue for development of more favorable absorption ratios. Is the affinity for P^{32} of new bone osteoid tissue and that of tumor tissue so great as to fix available phosphorus until none remains for the less competitive but radiation-sensitive hematopoietic tissues? Conversely, in the patient reported on, did the two transfusions immediately prior to therapy with P^{32} depress hematopoiesis and thereby favorably shift the differential absorption ratio in favor of the tumor and osteoid tissue?

One of us (C. C.) in preliminary experiments administered P^{32} to 50 DBA mice after bleeding and to 50 after hematopoietic depression with parenterally administered iron therapy. He was unable to demonstrate any consistent histological difference in the marrow as compared with that of control mice after use of P^{32} alone.

What factors might be clinically used in selecting patients for such therapy? Are roentgenograms showing osteoblastic metastases significant? Does a high alkaline phosphatase level indicate rapid bone formation and hence insure increased P^{32} uptake? The acid phosphatase level seems to indicate active extraprostatic cancer growth and should portend

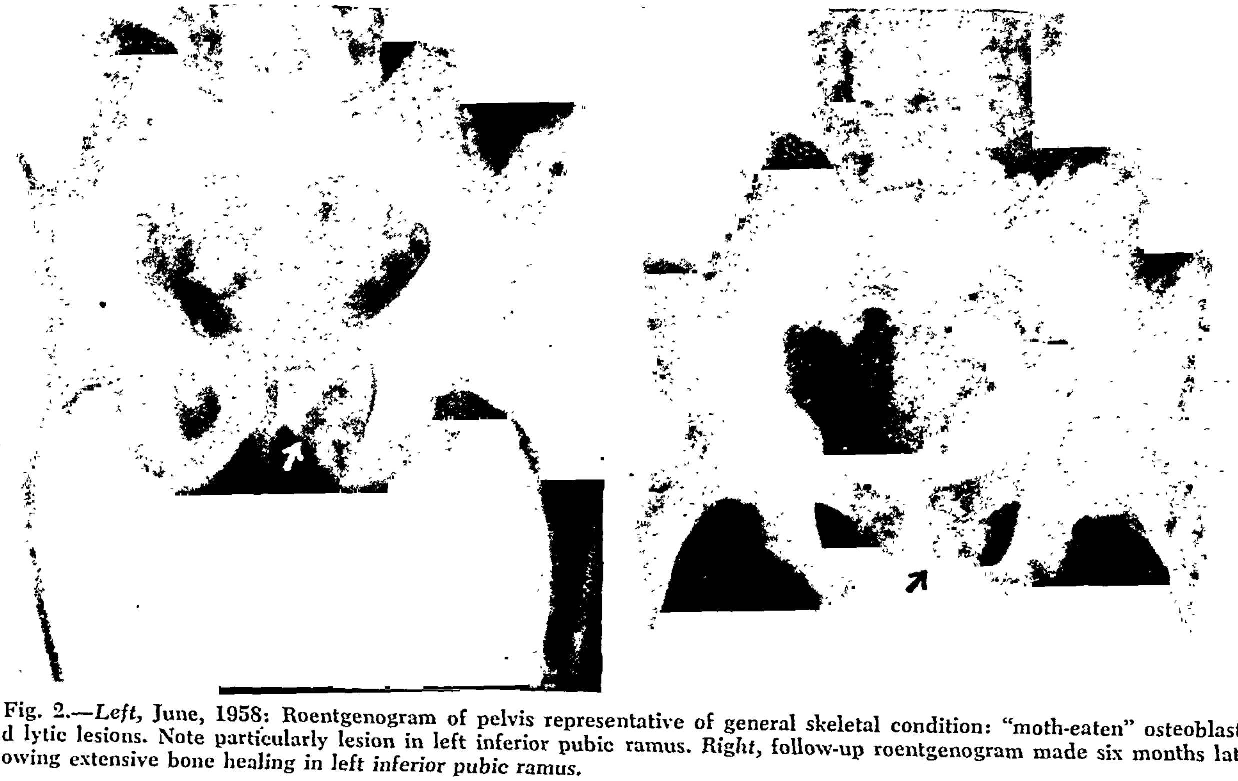

Fig. 2.—*Left*, June, 1958: Roentgenogram of pelvis representative of general skeletal condition: "moth-eaten" osteoblastic and lytic lesions. Note particularly lesion in left inferior pubic ramus. *Right*, follow-up roentgenogram made six months later showing extensive bone healing in left inferior pubic ramus.

increased uptake in the tumor. However, fibrinolysin titer, serum phosphorus level, and calcium studies followed no set pattern in either pretreatment or post-treatment evaluation. Should administration of estrogens be added to that of testosterone as suggested by Albright and Reifenstein?[8] Was the pain relief the effect of testosterone therapy alone as observed and reported by Munger?[10] None of our patients showed any decrease in narcotic requirements until after use of radioactive phosphorus. Is the observed effect due to physical degradation of the molecular structures into which P^{32} is incorporated—so-called hot chemistry—or the result of ionization from emitted radiations? In view of the observed new lesions appearing at the same time post-treatment healing is observed (fig. 3), should prolonged administration of P^{32} be considered? Does the irradiation of adjacent tissues inhibit their uptake of radioactive phosphorus? What is the most satisfactory balance between these two factors of drug administration? Would a low-phosphorus diet increase the demand for P^{32} by osteoid and tumor tissues?

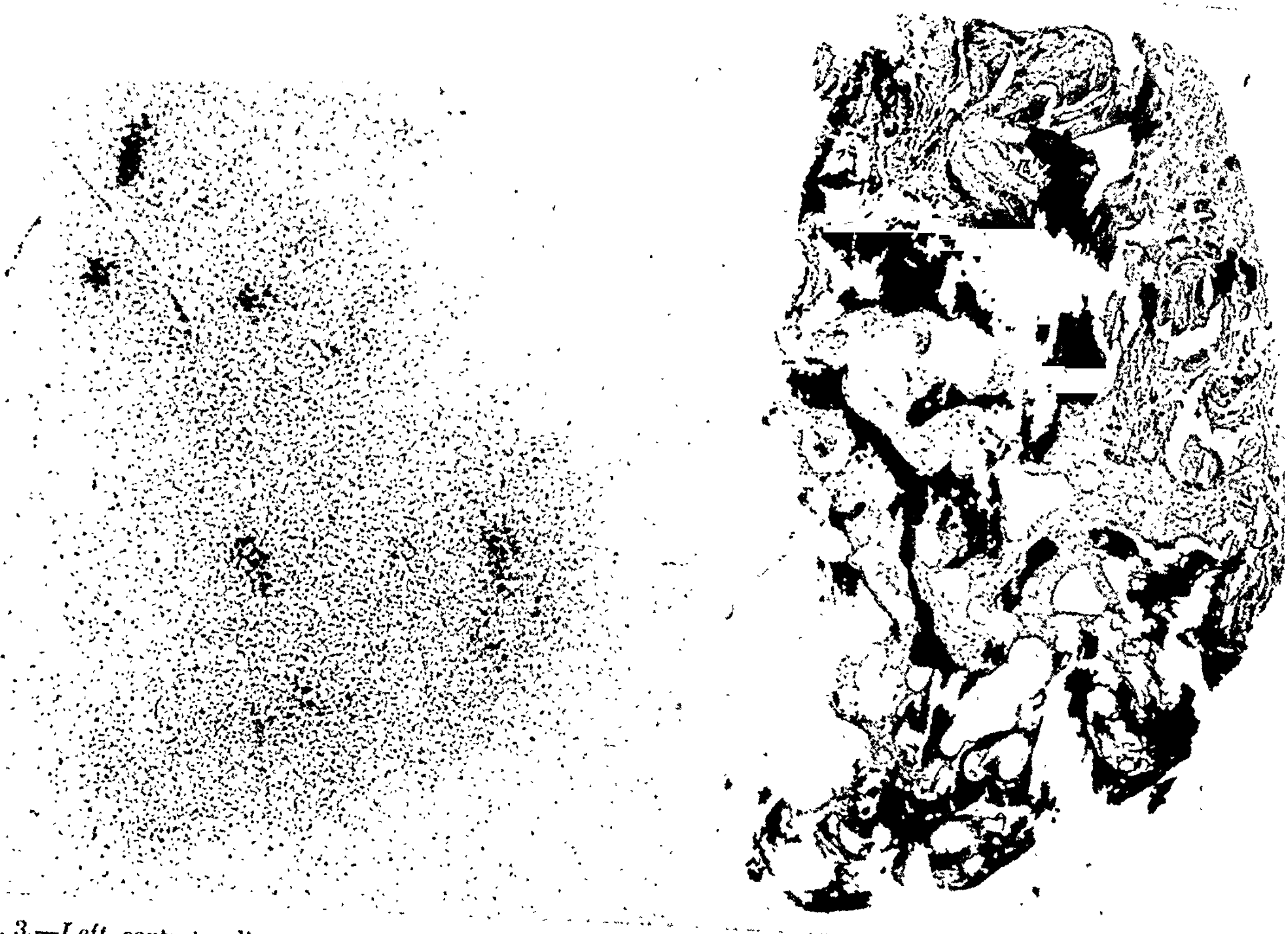

Fig. 3.—*Left,* contact radioautograph of adjacent histological section demonstrating osteoid uptake. *Right,* histological section from iliac crest lesion showing tumor and new bone formation. Note that most intense blackening of photographic emulsion at sites of osteoid rather than tumor.

Summary and Conclusions

Our aim is to add a few more cases to the growing group of patients reported in whom palliation of pain of disseminated cancer of the prostate has been achieved with radioactive phosphorus. No conclusions as to rate or quality of effect can be reached. The following intriguing observations, however, make continued investigation mandatory.

Extracellular deposition of radioactivity in the area of metastasis produced the desired effect. The original theory was that intranuclear incorporation of radioactive phosphorus would be most pertinent. The unexplained minimal hematopoietic inhibition suggests a blocking mechanism. Further investigation of hormone effect on tumor cells and stroma may demonstrate methods for increasing the ratio of differential absorption. Dietary and other physiological variations influencing the body pool of phosphates may also affect absorption. The rate of presentation of radioactivity must be balanced against the isoinhibitory effects on further uptake. The existence of this phenomenon is demonstrated by the depression of P^{32} incorporation in nucleoprotein after roentgen radiations.[11]

Even though, from the few cases presented, conclusions are not of great value, we hope the observations will be stimulating to the clinician in his search for greater aid to his patients.

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REPORT ON CARCINOGENIC ACTION OF CERTAIN AGENTS ON URINARY BLADDER OF DOGS

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Urinary bladder tumors were produced in four dogs by administration of para-aminobiphenyl. The time intervals from administration of the compound until tumors were observed ranged from 21 to 34 months. The pathological changes in all cases were those of medium-grade squamous cell carcinoma. Investigation of para-nitrobiphenyl was also carried out on four mongrel dogs. Three developed tumors of the bladder in 25, 33, and 33 months, respectively, but the fourth dog was still free from tumor after 33 months. Pathologically, the tumors produced in these dogs were essentially identical with the tumors produced in the dogs exposed to para-aminobiphenyl. The results corroborated the previous work of Walpole that para-aminobiphenyl is carcinogenic to the bladder of dogs and of Melick that the compound is carcinogenic to the human bladder.

It is not my intention to expound my philosophy regarding the practice of either medicine in general or urology in particular; on the contrary, I shall report on the results of several definite experiments carried out in the experimental laboratory to determine whether certain industrial chemicals are carcinogenic to the urinary bladder and comment on these results.

The present study is a group study which was initiated in September, 1952, under the direction of William B. Deichmann, Ph.D., F.R.S., then professor in the department of pharmacology at Albany (N. Y.) Medical College, and was continued to its conclusion at the University of Miami School of Medicine, where Dr. Deichmann came in 1953 to assume the chair of pharmacology. The department of pharmacology, the division of urology of the department of surgery, and the department of pathology collaborated in the projects.

Chairman's address, read before the Section on Urology at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 11, 1959.

From the Experimental Laboratories, University of Miami School of Medicine.

Because of its close chemical relationship to benzidine, a chemical known for some time to be carcinogenic to the human bladder, and because of its commercial importance in the chemical industry until recently, para-aminobiphenyl (Xenylamine) *was considered a possible* carcinogenic agent to the urinary bladder and was one of the chemicals selected for investigation. In addition, since para-nitrobiphenyl is an intermediate in the manufacture of para-aminobiphenyl, we were curious to learn whether this substance also might be carcinogenic. Experiments investigating this substance were started in 1955. In October, 1955, we also initiated studies of a third group of chemicals, the toluidines, for reasons that will be given in detail later. Although still another compound is under investigation at present, I shall not report on it since we have as yet no positive data.

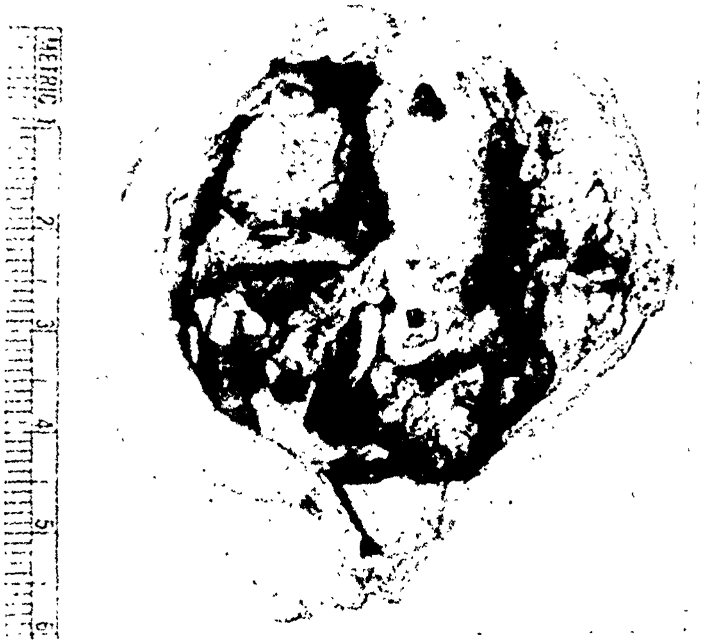

Fig. 1 (dog D-74).—Fed para-aminobiphenyl: urinary bladder, showing irregular papillary growth from mucosa and irregular thickening of bladder wall.

A preliminary report on the effect of para-aminobiphenyl fed to mongrel dogs was made by us in January, 1956,[1] and the final report was published in January, 1958.[2]

Experiments

Para-Aminobiphenyl.—Four healthy young adult female mongrel dogs were used for the para-aminobiphenyl study. The animals were secluded in pens with an area of 7 ft. by 9 ft., from which they were not released during the study, and thus were entirely isolated from any environmental factors that might affect the results of the experiment. Cystoscopic examinations were made at intervals of about four months.

Results: Tumors of the urinary bladder were produced in all four of the dogs that had been exposed to para-aminobiphenyl. The times from the start of administration of the compound until tumors were observed were 21, 29, 33, and 34 months, respectively. Administration of the chemical was continued in three of the animals for three to nine months after appearance of the tumors. All died in from 4 to 13 months after discovery of the cancers of the bladder. Findings of intoxication remained essentially negative until tumors appeared. The only consistent observation was hematuria, severe in one dog but mild in the other three. Salivation, loss of weight, and vomiting were noted, but always in a mild form. The total quantity of para-aminobiphenyl ingested by each dog up to the date of appearance of the tumor was, respectively, 87.5 Gm. (8.2 Gm. per kilogram of average body weight), 129.5 Gm. (9.6 Gm. per kilogram of average body weight), 94.5 Gm. (8.4 Gm. per kilogram of average body weight), and 144 Gm. (14.1 Gm. per kilogram of average body weight).

The pathological description of these tumors of the bladder was consistent. Most typical was the report on dog D-74, "Grossly, the most prominent feature was the presence of polypoid projections of the mucosa. The polypoid mucosal thickenings obscured the ureteral openings, which were not identifiable (fig. 1). On section, the polyps were composed of rubbery grayish-white tissue with areas near the surface that were a darker gray and somewhat friable. The muscular wall of the bladder was thickened. Microscopic examination showed varying degrees of mucosal hyperplasia, with areas of neoplastic transformation. The hyperplastic mucosa showed areas of squamous metaplasia. The areas of carcinomatous change showed variable appearance. In some portions a papillary or glandular arrangement or architecture was maintained, but in other areas there was a change to a predominantly squamous type of neoplasm, although keratinizing activity was not a prominent feature. In some of these areas the tumor cells showed striking variation in size, shape, staining properties, and arrangement. Some giant tumor cells were present, and a moderate amount of mitotic activity was evident. There was invasive activity, with infiltration in irregular columns between muscle bundles deep in the bladder wall. The changes were evidently those of a medium-grade malignancy and a predominantly squamous cell carcinoma (fig. 2 and 3). At autopsy one dog showed marked hydronephrotic change, with moderate to severe renal damage as a result of obstruction to the ureters by the tumor growths in the bladder—a picture which fits the classical description of squamous cell carcinoma of the human urinary bladder."

Para-Nitrobiphenyl.—Investigation of para-nitrobiphenyl (started in December, 1955) was also carried out on four healthy young adult female mongrel dogs. In addition to the chemical, the animals were fed a diet consisting of wet wheat and bone meal, ground beef or horse meat, and dog crackers. Para-nitrobiphenyl (Eastman reagent grade), in doses of 0.3 Gm., was administered by cause many studies have demonstrated that purebred strains of animals may show a degree of sensitivity or even susceptibility to certain chemical irritants that is not shown by mixed strains. Furthermore, since man is definitely a mongrel animal, it was again our desire to approximate man as nearly as possible in our experiment.

Young adult dogs were selected, in anticipation of a long-term program. Our thinking was based on previous studies, which had disclosed that exposure of both dog and man to the aromatic amines did not result in early carcinogenic effects.

Female dogs were chosen for the study merely as a matter of convenience, since they can be subjected to cystoscopy with ease. We did not think that the difference in sex would in any way affect the carcinogenic behavior of the compounds if, in fact, they proved to possess carcinogenic properties. Our view is, however, contrary to that of Boyland.[8]

During the course of our experiment with para-aminobiphenyl, we became aware of the study by Walpole and co-authors[6] on the effect of this agent on two male beagles. Walpole's studies differed from ours in that he used purebred animals of greater susceptibility, while we worked with mongrels. Also, at no time during his investigation had he performed cystoscopy on the dogs to determine what, if any, changes might be taking place in the mucous membrane of the bladder before the actual development of the tumors which he and his associates discovered post mortem.

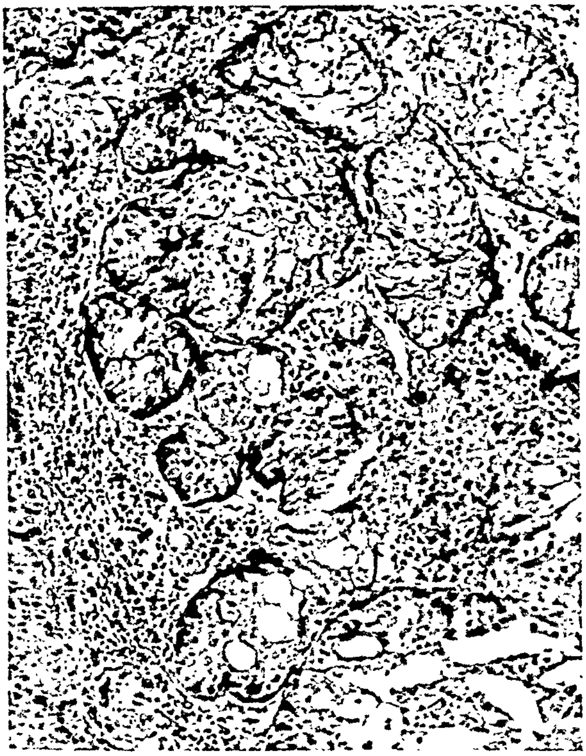

Fig. 5 (dog D-70).—Biopsy specimen of urinary bladder, showing epithelial tumor growth (× 102).

Our study confirmed the report of these authors[6] as regards the carcinogenicity of para-aminobiphenyl to the urinary bladder of the dog. There was only a slight variance in the period between the start of feedings and the appearance of the tumors in the dogs of Walpole and others and of Deichmann and others, despite the fact that there was an interval (Jan. 1, 1952, to June 1, 1952) in which the dogs of Walpole and others were not fed any of the compound. One point of the findings of Walpole and his associates deserves comment. Having reported that the tumors which developed in the bladders of their dogs were on the dome and the posterior wall, the impression might be gained from this statement that para-aminobiphenyl may have a selective action on a particular area of the bladder mucosa. Our study, however, revealed tumor growths to have no particular location within the bladders of our four dogs; tumors were found on the trigone and the lateral walls as well as on the dome and the bladder floor. The observations of Melick and co-workers[7] in the human bladder coincide with these findings.

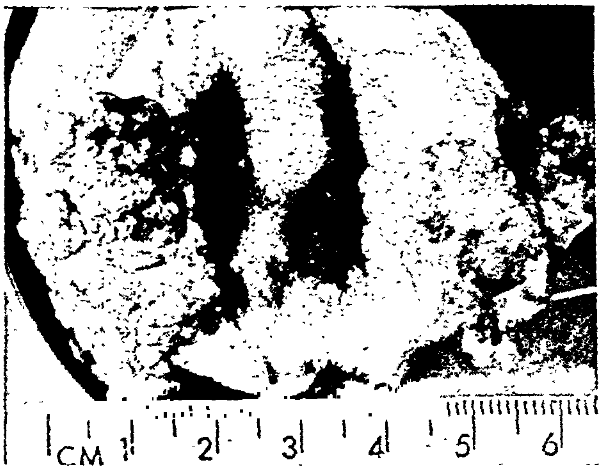

Fig. 6 (dog D-37).—Fed para-nitrobiphenyl: urinary bladder, showing small and large polypoid tumor masses.

The observations by Melick and co-workers[7] on the carcinogenicity of para-aminobiphenyl in human subjects were presented before the Convention of the American Urological Association, Los Angeles, May 16-19, 1955. It is regrettable that Melick's paper was not discussed at that time and that the results of the present experiment with this compound on dogs were not reported, since our study was already completed. While Melick and co-workers had reason to assume that para-aminobiphenyl was the causative agent that produced the cancer of the bladder in their subjects, they nevertheless lacked the experimental proof that "pinpointed" para-aminobiphenyl as the carcinogenic agent. Undoubtedly, these persons had also been exposed to other chemicals in their industrial environment. We believe that our results have given support to their major role in the manufacture of these dyes. The acute toxic effect of these chemicals on man was recognized early, but the delayed effects of some of the amines were not suspected until Rhen, in 1895, reported findings of tumors of the urinary bladder in four men who were working in the manufacture of magenta (basic fuchsin). Rehn's theory that these tumors resulted from some particular environmental factor was not readily accepted. However, his report did stimulate a wave of investigation. In 1898, Leichtenstein was the first to attribute cancer of the bladder to naphthylamine. In 1921, beta-naphthylamine was implicated as a carcinogen to the bladder. Additional proof that this compound is carcinogenic was presented in 1937 by Hueper and Wolfe[3] and 1938 by Hueper and co-workers.[4] For many years aniline was considered the carcinogen responsible for the tumors of the bladder found in workers in the dyestuff industry, but much evidence has since accumulated to indicate that other amines that are used in conjugation with aniline in the manufacture of dyes are the actual carcinogens. In 1950, Spitz and co-workers[5] demonstrated that benzidine was carcinogenic to the urinary bladder of both rats and dogs.

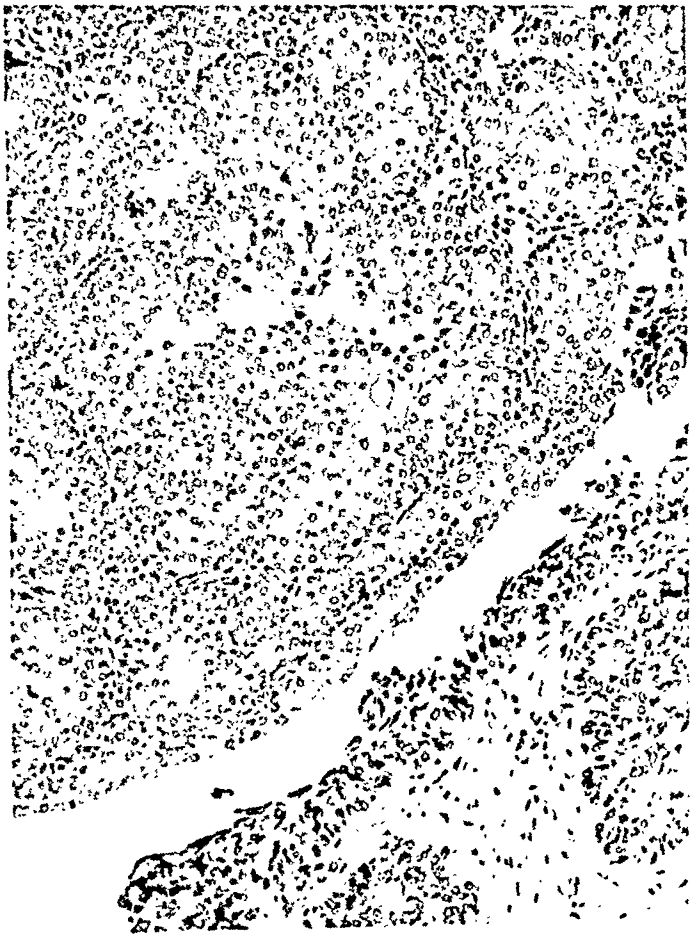

Fig. 3 (dog D-74).—Urinary bladder, showing papillary tumor of mucosa with squamous differentiation (× 102).

Walpole and co-workers[6] reported on the carcinogenicity of para-aminobiphenyl in the bladder of the rat in 1952 and in the canine bladder in 1954. They predicted that tumors of the bladder would occur in men exposed to this chemical. Melick and co-workers[7] proved their forecast to be of merit when, in 1955, they reported findings of tumors of the urinary bladder in 19 men engaged in the manufacture of para-aminobiphenyl. It may be recalled that the first report on this study[1] on para-aminobiphenyl was published in 1956. In July, 1958, Deichmann, at the Seventh International Cancer Congress in London, announced the carcinogenicity of para-nitrobiphenyl to the canine bladder. These historical data represent but a few stages in the search for the true bladder carcinogens that has been going on for years.

Comment

Dogs were selected as subjects for our study, because previous investigations with benzidine and beta-naphthylamine had revealed the dog to be the animal of choice, presenting an almost perfect human counterpart for studies on the urinary bladder. The histological and functional structure of the urinary bladder in man and dog are similar, and the carcinoma produced in both human and canine bladders after exposure to benzidine and beta-naphthylamine presents a histological lesion almost identical with the carcinomatous lesions found in the human bladder in our day-to-day clinical practice.

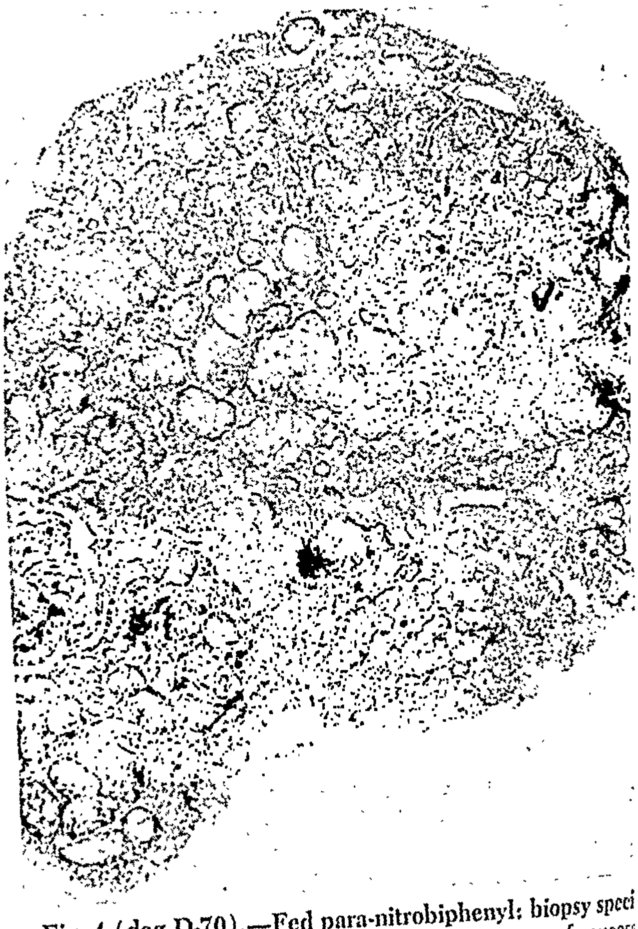

Fig. 4 (dog D-70).—Fed para-nitrobiphenyl: biopsy specimen of urinary bladder, showing papillary tumor of mucosa with squamous differentiation (× 30).

Our subjects were mongrel dogs, rather than inbred strains such as the beagle used in the experiment executed by Walpole and co-workers,[6] be-making an existing product better or cheaper or for their use in the creation and manufacture of new products. More and more persons are being employed in the production of these chemicals and in the factories where these compounds are used in the development of new marketable products. The consumer is exposed to many old and new chemicals the effects of which on the human body may not be known for years to come, so slow and insidious are the actions of some.

At present only a few of the many chemicals used in industry are known to be carcinogenic in the bladder of man and dog. Bonser and co-workers [15] listed only five such agents as definitely established and then added para-aminobiphenyl on the strength of the report by Melick and co-workers.[7] They stated, "It would be surprising if the five chemicals listed above proved to be the only substances capable of inducing bladder cancer in man in our increasingly technological environment." We at the University of Miami certainly agree, or, as Deichmann has said repeatedly, "It is high time that we put our primary effort on the prevention of cancer, and that we seriously consider the chemical constitution and metabolism of additional industrial compounds as well as agents in our daily diet, because the compounds primarily responsible for human bladder cancer have not yet been discovered." The report by Steiner [16] supports this statement and emphasizes that most patients with cancer of the bladder could not have been exposed to the few known bladder carcinogens. The Steiner report revealed that of the 6,072 patients with cancer admitted to the Los Angeles General Hospital between 1918 and 1947, cancer of the urinary bladder ranked 10th in the list of organs and other structures affected.

Melicow [17] pointed out the marked resemblance of all tumors of the bladder to the tumors in two of his patients who had been exposed to aniline dyes, and he asked if there might not be some similar carcinogenic agent that also induces cancer of the bladder in the general population by activation of the urothelium in these vulnerable persons. Scott and Williams [18] phrased the question differently but actually made an inquiry based on the same theory.

That urologists must support any investigation that has to do with research on cancer of the bladder should not have to be emphasized. But even more important is our duty to investigate thoroughly every epidemiologic possibility in the large number of cancers of the bladder that come under our observation and care each year. Does our interest in these tumors lie purely in their recognition and treatment? I fear that in most instances we are guilty as charged by the question.

Summary

Experimental proof, presented here, establishes the carcinogenicity of two aromatic amines, namely, para-aminobiphenyl and para-nitrobiphenyl, to the urinary bladder of the dog. One of our experiments, that with aminobiphenyl, lends supporting evidence to the report by Melick and co-workers [7] on the carcinogenic action of this compound on the human bladder. Our investigations also confirm the opinions of other workers in the field of cancer research that the bladder carcinogens in both man and dog require long periods to manifest their effects after initial exposure to the agent.

The principal investigator associated with this study, W. B. Deichmann, for the first time announced to the clinical profession, at the Seventh International Cancer Congress in London in 1958, the proved existence of another carcinogen, para-nitrobiphenyl, to the bladder of dogs. We are offering the assumption that this compound is carcinogenic also to the urinary bladder of man. Our investigation into the possible carcinogenic or noncarcinogenic effect of certain toluidines on the canine bladder is not yet sufficiently advanced to permit presentation of definite data.

The history of the investigation of tumors of the bladder during the past half-century, which started in the 1850's with an awareness of the hazards presented by dyestuff manufacture from coal tar, confirms the need for a greater interest on the part of urologists (and members of the medical profession in general) to ascertain the possible epidemiologic factors in all patients with tumor of the bladder which come under their care; mere establishment of a diagnosis and treatment of these tumors does not constitute an adequate approach.

We preferred the use of mongrel dogs for several definite reasons. Our results obtained with these dogs, despite some divergences in other aspects, corroborated the findings (1) of Walpole and coworkers (who used purebred dogs) that para-aminobiphenyl is carcinogenic to the bladder of dogs and (2) of Melick and co-workers that the compound is carcinogenic to the human bladder.

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Messrs. J. L. Radomski, Ph.D., and W. M. McDonald, M.S., and Drs. Frank M. Woods, John Heslin (Albany Medical College, Albany, N. Y.), and W. A. D. Anderson were members of the team that performed the studies reported.

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contention, gained from clinical observation, that para-aminobiphenyl is carcinogenic to the human bladder and that the effect of exposure to it is delayed far beyond the immediate period of exposure.

We are in full agreement with Walpole and co-workers,[6] Hueper and co-workers,[8] and Melick and co-workers[7] that the tumors produced in our dogs were definitely invasive. And we are in agreement with Walpole and associates that these tumors do not tend to metastasize, since neither the dogs of Walpole and others nor those of Deichmann and others showed any evidence of metastasis at autopsy.

The human subjects reported on by Melick and others showed few clinical symptoms except hematuria, which we found to be true also in our animals. The cystoscopic appearance of the human bladders, as described by Melick and co-workers,[7] varied from absence of detectable changes in the mucous membrane to marked areas of ecchymosis, engorgement, or both, of the mucosa prior to actual development of the tumor growth. The pretumor phases in our canine bladders revealed precisely these same variations.

Melick and associates reported one case of tumor which developed in the ureter and one in the renal pelvis. We found no tumors outside the bladder in any of our animals. The absence of tumors in the upper urinary tract in our dogs and the findings by Melick and others of tumors in the upper tract in two of their patients might be explained on the basis of experiments carried out by McDonald and Lund[10] and also by Scott and Boyd[11] and by the assumption expressed by many other investigators that the carcinogenic agent or its metabolite must be carried by the urine to the bladder or placed therein to come directly into contact with the mucous membrane. The urine containing the carcinogen must remain in contact with the mucosa sufficiently long to produce irritation. Although our dogs showed massive tumor growths in the bladder, one of them having the ureters partially obstructed to a degree which produced bilateral hydronephrosis, they died or were killed before the carcinogen-contaminated urine, lying stagnant in the upper urinary tract, had time to produce sufficient irritation to the mucosa thereof. On the other hand, the patients described by Melick and associates may have remained alive long enough, with obstruction to the upper tract produced by tumors of the bladder, to permit the carcinogen in the urine to have effect on the mucous membrane at a site above the bladder.

Several workers in the field of cancer research had suggested that para-nitrobiphenyl might be a bladder carcinogen in dogs and human subjects, but no experimental proof was provided until, in July 1958, Deichmann and others[12] announced the results of our studies on dogs. The detection of para-nitrobiphenyl as a bladder carcinogen in dogs poses an interesting question. As stated previously, this agent is an intermediate in the manufacture of para-aminobiphenyl. Therefore, we ask ourselves, were the tumors of the bladder that had been produced by exposure of both man and dog to para-aminobiphenyl the result of this specific chemical alone, or could they have resulted partially from exposure to para-nitrobiphenyl?

The mode of action of the carcinogenic amines has been a matter of investigation and speculation for years, the literature being replete with many splendid articles on the subject. The scope of this thesis does not permit inclusion of a detailed reference thereto, but recognition should be given to the suggestion submitted by Clayson[13] and to the postulate expounded by Walpole and co-workers.[6] Clayson thought that the carcinogenic process of the aromatic amines depends on their conversion to ortho-hydroxyamines. Walpole and co-workers have postulated that only those aromatic amines exhibit carcinogenic properties which are capable of forming ortho-hydroxy metabolites. In other words, it seems to be their opinion that it is possibly the ortho-hydroxy metabolites of certain aromatic amines, rather than the organized amines coming in contact with the bladder mucosa, which are responsible for the production of cancer of the bladder in man and dog.

It was deemed most important by us to obtain further proof of or to disprove this concept. It was for this reason that we initiated an experimental investigation with ortho-toluidine, meta-toluidine, and para-toluidine. These compounds were selected on the basis of the ortho-hydroxyamine-metabolite postulate that ortho-toluidine, but neither meta-toluidine nor para-toluidine, must be carcinogenic. The basis for this assumption is that ortho-toluidine is metabolized primarily to 2-amino, 3-hydroxy toluene, an ortho-hydroxyamine, whereas the meta and para compounds are metabolized to the corresponding aminobenzoic acids. The economic importance and wide use of these compounds was but another basis for their inclusion in our studies.

Reports in the literature to the effect that ortho-toluidine is a direct bladder irritant which produces acute hemorrhagic cystitis and vesicle tumors, and other reports attributing to this compound the faculty to produce metaplasia, keratosis, and papilloma in the bladders of rats strengthened our desire to investigate it as a possible carcinogen in dogs. Lastly, the report of Scott[14] of a tumor which developed in a human bladder after long exposure to ortho-toluidine excited our interest.

What does the foregoing mean to urologists? We are living in an age whose industrial and chemical character is expanding rapidly and far beyond our conceptions. New chemicals are being discovered almost from day to day. Industry absorbs them as rapidly as they are discovered for the purpose of

In some cases it may be advisable to make a more accurate evaluation by urethrography. A preliminary scout film is first taken, then a radiopaque fluid such as 40% iodopyracet (Diodrast) mixed with equal parts of a water-soluble lubricating jelly is injected into the meatus and through the urethra. Irregular feather-like projections of the fluid outside of the urethra indicate rupture of the urethra and extravasation of the fluid. If the patient has voided after the injury, urinary extravasation is presumed to have occurred as revealed by the urethrogram. When the patient has gone without treatment for a day or more, the skin over the areas of urinary extravasation is tense, shiny, inflamed, and hot, and the patient has toxic symptoms.

Treatment.—In order to prevent urinary extravasation after urethral injury, treatment must be given before the patient voids. Urinary drainage from the bladder is of primary importance. When the injury is mild and a catheter can be passed through the urethra, it is left in place for 12 days; surgical intervention is usually not necessary in these patients. If a catheter cannot be passed into the bladder, immediate surgery is indicated as follows: (1) simple suprapubic cystostomy, if the patient is a poor surgical risk and there is no urinary extravasation; (2) suprapubic cystostomy and antegrade sounding for manipulation with a sound passed through the anterior urethra in an attempt to realign the severed ends of the urethra and to pass a catheter through its injured portion; (3) exposure of the injured urethra through a perineal approach and anastamosis of the severed ends, if the proximal end can be identified; a catheter is passed through the urethra and left indwelling; (4) perineal approach, and if the proximal end of the urethra cannot be identified, cystostomy is done for antegrade sounding to identify the proximal end; (5) multiple incisions to establish free drainage of all extravasated tissue when there is urinary extravasation; and (6) in the absence of extravasation both the perineal and the suprapubic wounds can be closed tightly and all spaces obliterated except for a small prevesical rubber tissue drain; an indwelling urethral catheter is sufficient for bladder drainage.

Complications.—The patient with a straddle injury of the urethra is rarely in a state of shock unless there are other injuries. In some patients hemorrhage from the urethra and into surrounding tissues is severe enough to require transfusion. Infection and toxic symptoms from extravasation occur when treatment is delayed for more than 24 hours.

Sequelae.—Urethral strictures nearly always occur after straddle injury of the urethra. The stricture may be long, hard, and difficult to keep dilated. Accurate approximation of the urethral mucosa at the time of repair minimizes the seriousness of the subsequent stenosis. Sexual impotence often follows straddle injury, probably because of pudendal nerve injury.

Thirteen patients with straddle injuries have been treated at the Los Angeles County Hospital during the past five years. Urethrography was necessary for diagnosis in only one. Eleven patients were treated without surgery, while perineal repair only was necessary in one. One patient had a periurethral abscess and four years later had urethral strictures. There were no deaths. Six patients were lost to follow-up.

Injuries of the Pendulous Urethra

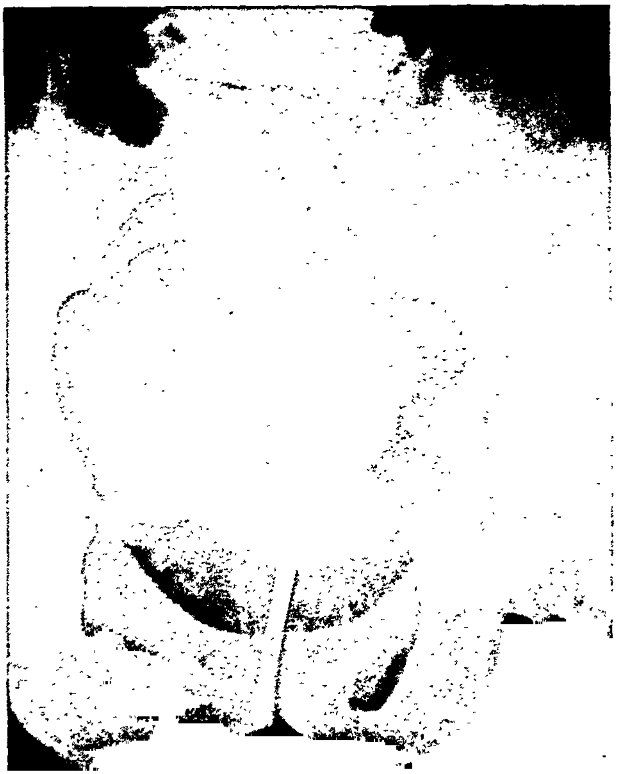

Fig. 1.—Rupture of prostatic urethra. Irregular feather-like projections of radiopaque fluid around urethra indicate extravasation. When bulbous urethra is ruptured, extravasation is below pubis.

The pendulous urethra is infrequently subjected to serious injury. The most common cause is a kick during a fight. While a boy is passing his urine into a toilet bowl, the lid may fall on his penis and injure the urethra. Excessive manipulation for sexual gratification can cause urethral injury. Crushing, penetration by missiles, and other forms of external injury occur. Most of these are treated with a simple indwelling urethral catheter and usually result in more or less stenosis. The 14 patients seen at the Los Angeles County Hospital during the past five years were all treated by indwelling catheter. Two women had lacerations of the urethral meatus, which were repaired.

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INJURIES OF THE URINARY TRACT DUE TO EXTERNAL TRAUMA

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Early examination and accurate diagnosis in urinary tract injuries are essential to obtain best results from treatment. Extravasation of urine must be prevented or treated immediately. Roentgenographic studies are usually necessary. Of 13 patients with straddle injuries in a five-year period, 11 were treated without surgery, while perineal repair was necessary in only one. Urethrography was needed for diagnosis in but one case. Insertion of an indwelling catheter sufficed for 14 patients with injuries of the pendulous urethra. Thirteen of 15 patients with ruptured or transected injuries of posterior urethra required surgery. All but one of 54 patients with bladder injuries required surgery. Five ureteral injuries caused by gunshot wounds were repaired and splinted with good results. Of 126 patients with renal injuries, 62 were treated with conservative measures. The others required surgery.

When the urinary tract is injured it is important to make an early and accurate assessment of the extent of the injury. Physical examination of the patient may give sufficient information to direct treatment, but roentgenographic studies are usually necessary.[1]

Straddle Injuries

Cause.—Straddle injuries are caused by falling astride a hard object and crushing the urethra against the undersurface of the pubic arch, which sometimes shears it completely across.

Diagnosis.—Bloody urethral discharge usually occurs when the injury is slight; there is often hemorrhage from a severe injury. Ecchymosis or laceration, or both, of the perineal skin and swelling of the subcutaneous tissues are usually found. There is often obstruction to the passage of a catheter and such manipulation increases the bleeding. Any one of the above findings is sufficient to warrant a diagnosis of urethral injury and to indicate institution of therapy.

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erted through the vesical orifice (fig. 3). If the bladder is torn from the urethra a 24-French 30-cc. Foley bag catheter is passed through the urethra nto the bladder and traction is applied to approximate the torn edges. It is not necessary to identify and close extraperitoneal ruptures of the bladder; they heal without suture. Rubber tissue drains are nserted into the perivesical space to emerge through he lower edge of the suprapubic incision. The incision in the bladder is closed completely with two ayers of 000 chromic catgut. It is seldom necessary o leave a catheter in through the suprapubic openng; the urethral catheter drains the bladder adequately.

Results and Sequelae.—Excessive fibrosis may result in stenosis of the prostatic urethra or bladder neck, or both. Other complications and sequelae re rare. There may be sexual impotence. A spicule of bone occasionally remains in the bladder or unexplained infection may persist.

Fifteen patients with ruptured or transected injuries of the posterior urethra were treated at the Los Angeles County Hospital during the past five ears. Only two of these could be treated without peration. Three patients died of other injuries. There were 54 patients with bladder injuries (table), 31 of which were ruptured. Four of these paients were moribund when they were admitted to he hospital and all but one of the rest required urgery.

Injuries of the Ureters

The ureters are less frequently injuried by exernal trauma. Penetrating wounds such as those rom missiles or sharp instruments may involve the ureter. Excretory urography usually shows extravaation of radiopaque fluid through the ureteral deect. A positive diagnosis is made when the retrograde ureterogram shows extravasation. The injury repaired by anastamosing the spatulated ends of he injured ureter, if there is sufficient length; if ot, the kidney is destroyed when the contralateral ne is normal, or a segment of ileum may be subituted for the ureter if the other kidney is disased or absent. There were five ureteral injuries aused by gunshot and treated at the Los Angeles ounty Hospital during the past five years; four ere recognized immediately while one was recogzed by the appearance of a fistula on the 10th ay. All were repaired and splinted with good sults.

TABLE 1.—*Patients Admitted to Los Angeles County Hospital With Bladder Injuries*[*]

Injury, Type	Patients, No.	Died Before Operation	Repair
ntusion	16	0	0
pture	31	4	26
abbing	1	0	1
nshot	6	0	6
Total	54	4	33

[*] Six patients with rupture of the bladder died from other injuries.

Injuries of the Kidney

Causes.—Any severe blow to the lumbar region may contuse the kidney. Riding toboggan sleds, playing football, and boxing are the most hazardous sports for causing renal injury. Automobile accidents are near the top of the list as a causative agent. Perforating injuries are more rare.

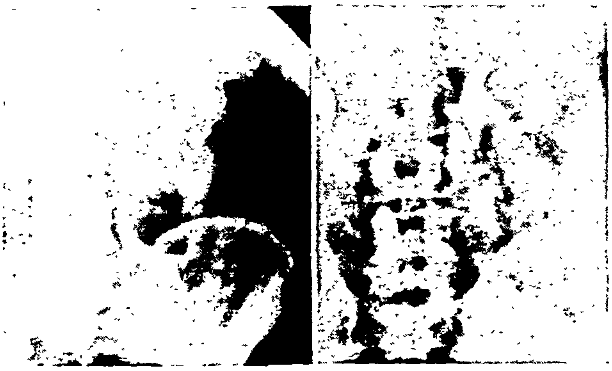

Fig. 4.—*A*, excretory urogram showing extravasation through ruptures in left kidney. *B*, excretory urogram made one month after injury. Conservative, nonsurgical treatment was used.

Symptoms.—Symptoms vary from only slight tenderness in the lumbar region and a few red blood cells in the urine to severe tenderness, grossly bloody urine, and sometimes a palpable mass due to hematoma in the perinephritic space; however, pain in the lumbar region and blood in the urine are the chief symptoms of renal injury. Symptoms of shock occur when the injury is severe or when other organs are involved, or both.

X-ray examination is indicated in most cases and is essential when surgery is contemplated. Excretory urogram studies are usually sufficient; they show whether or not the uninjured kidney is present and normal and they usually demonstrate urinary extravasation, if it is extensive enough to be significant (fig. 4, left). The radiopaque fluid extends outward from the pelvis or calyces, or both, and may reach the perinephritic space. If the excretory urograms are unsatisfactory, retrograde pyelogram studies are indicated.

Treatment.—Most kidney injuries can be treated conservatively. Sedation, bed rest, and application of an ice bag to the lumbar region are sufficient for patients with mild renal contusion. Treatment of shock, including blood transfusions, is necessary for those with more severe injuries. When there is such evidence of continued loss of blood as massive hematuria, enlarging lumbar mass, recurrent shock after blood replacement, and increasing rapid thready pulse, operation is indicated. In these patients, removal of the damaged kidney is nearly always necessary. Most kidneys which are not damaged beyond repair do not develop symptoms or findings, or both, which are severe enough to indicate surgical intervention. Sometimes a portion a contused kidney is removed when the r

Injuries of the Membranous Urethra

The membranous urethra is short, deep in the perineum, and protected by the tough triangular ligament. It may, however, be injured by a bony fragment of a fractured pelvis or by penetrating objects. There is usually also injury to both the bulbous and the prostatic portions of the urethra, and urethrography shows extravasation both proximal and distal to the triangular ligament. Treatment is the same as that used for both anterior and posterior urethral injury. Urinary incontinence is sometimes a sequela. Both this and intractible urethral stricture may be successfully treated by a plastic surgical procedure in which the bulbous urethra is freed and excised at its junction with the membranous urethra, then pulled upward through the membranous urethra and sutured to the bladder neck.

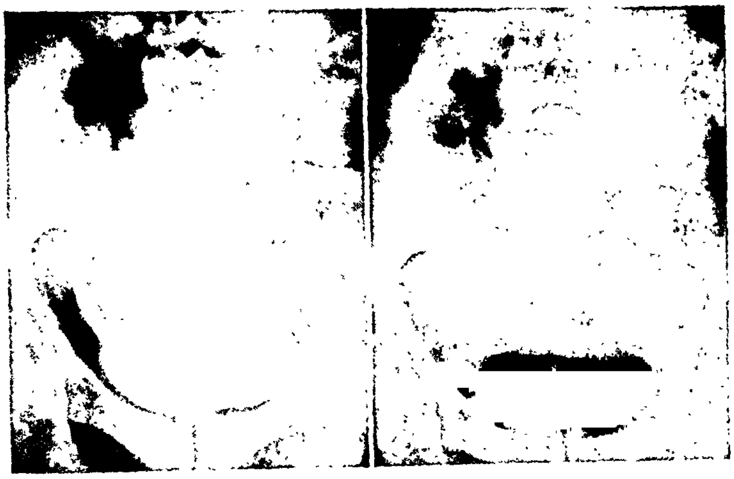

Fig. 2.—Cystogram, showing extravasation of radiopaque fluid into peritoneal cavity; intraperitoneal rupture of bladder.

Injuries of the Prostatic Urethra and Bladder

Causes.—The prostatic urethra or the extraperitoneal area of the bladder, or both, are often injured when the pelvis is fractured. A fragment of bone perforates the viscus and urinary extravasation usually occurs. Missiles or other piercing objects are less frequent causes.

Symptoms and Findings.—There is severe suprapubic pain, usually inability to void, and sometimes bloody urethral discharge. The patient is in shock, more or less, and if not treated toxic symptoms soon develop from the extravasated urine.

On examination tenderness, rigidity, and dulness to percussion over the suprapubic region are revealed, and sometimes an indefinite mass is palpable. When the injury involves the prostatic urethra, the catheter is usually obstructed at that point. If the catheter can be passed into the bladder, blood or bloody urine is obtained. When a measured quantity of sterile saline solution is injected into the bladder, some of it may extravasate through the rupture in the viscus and a smaller quantity will be recovered than was injected. The perforation may be sealed, however, and this test be negative. Urethrography performed after injection of radiopaque fluid through the catheter, whether it can be passed into the bladder or not, will show extravasation if rupture has occurred (fig. 1). When there is intraperitoneal rupture, the radiopaque fluid is seen in the peritoneal cavity (fig. 2).

Treatment.—The prevesical space is entered through a suprapubic incision. Clots are removed and extravasated urine is aspirated. An incision is made through the peritoneum and if bloody fluid is found in the peritoneal cavity exploration for intraperitoneal injury is indicated. The peritoneum covering the bladder is examined and if a perforation is found it is closed with three layers of 000 chromic catgut, inverting the bladder edges. Mor extensive exploration for other intraperitoneal injuries is usually indicated, especially if there i blood in the peritoneal cavity and no intraperitc neal injury of the bladder is found. After the inc sion through the peritoneum is closed, the blad is opened, clots are removed, and its wall is amined from within for possible intraperitoneal r ture. If one is found, the edges are grasped w Allis forceps, pulled into the bladder, and sutu together with two layers of over-and-over 000 c mic catgut. A catheter over a stylet is passed i the bladder—it can be guided with the finger tip

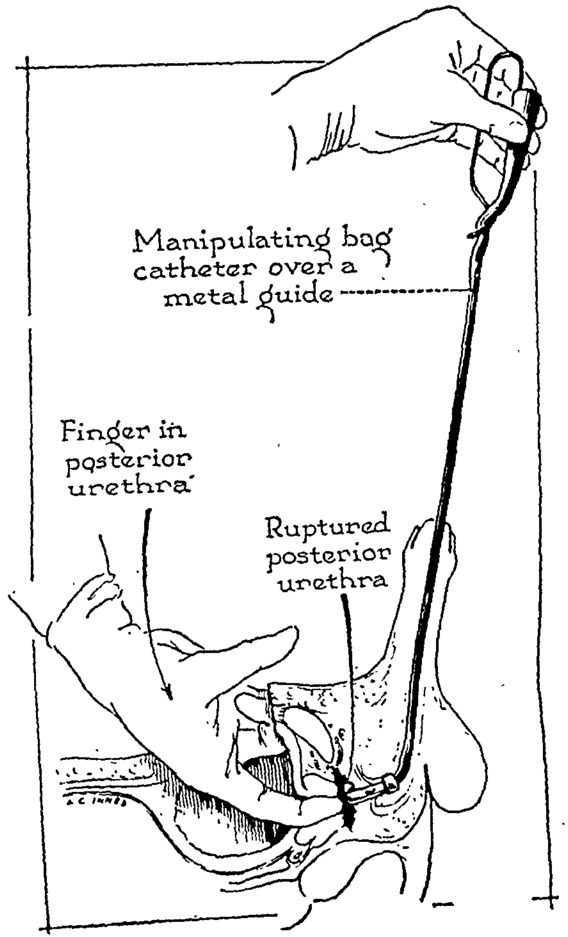
Manipulating bag catheter over a metal guide
Finger in posterior urethra
Ruptured posterior urethra

Fig. 3.—Finger through suprapubic cystostomy is manipulated with sound passed through anterior urethra. Attempt is made to realign severed ends of urethra and pass catheter through it. (Reprinted from Urological Practice by R. W. Barnes and M. L. Hadley; with permission of the C. V. Mosby Company.)

AMPHETAMINE, SECOBARBITAL, AND ATHLETIC PERFORMANCE

III. QUANTITATIVE EFFECTS ON JUDGMENT

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and
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Fifteen college swimmers, in midseason condition, swam 360 time trials after receiving 100 mg. of secobarbital, 14 mg. of amphetamine, or placebo on different occasions. After each trial a swimmer estimated his performance time and gave a detailed evaluation of his performance. Secobarbital significantly impaired performance, and amphetamine significantly improved it. The subjective data showed that secobarbital produced distortion in judgment; after taking secobarbital the swimmers thought their performances were unusually good, whereas in fact they were unusually bad. The effects of amphetamine on judgment were not conclusive.

Numerous laboratory investigations have shown that barbiturates and other drugs alter performance on psychomotor and mental tests.[1] The present investigation provided a rarely available opportunity to study a complex mental function in a situation allowing quantitative precision and laboratory controls to be combined with "real life" conditions which avoided the artificiality of a laboratory experiment. By comparing an athlete's actual performance with his estimate of his performance, it was possible to examine a complex process of judgment in a situation in which the factors studied, performance and judgment, appeared to be matters of personal importance to the subject. An additional advantage was that each subject was a highly trained athlete in midseason form who was skilled in estimating his performance time.

The investigation reported here was designed, primarily, to determine whether amphetamine sulfate improved the performance of trained athletes and to determine the subjective effects of amphetamine on such athletes. Data pertaining to these two questions have been reported elsewhere.[2] The data reported in the present paper concern the effects of amphetamine and secobarbital on judgment.

Method

Fifteen members of a college swimming team swam twice each day on 12 consecutive days during the middle of their swimming season. Three of the men swam the 100-yd. butterfly, three the 100-yd. free style, three the 200-yd. breast stroke, three the 200-yd. free style, and three the 200-yd. backstroke. On six days each man swam alone ("solo" trials) and on six he swam in a group of three ("group" trials). When swimming in groups a subject competed with two other members of the team whose usual speeds, in comparison with his own, he knew. The second swim of each day began 15 minutes after the beginning of the first and so was performed under conditions of fatigue. All trials occurred during the late afternoon. Each swimmer was timed by two or more clocks (standard stop watches and an electric timer) on all trials.

Each subject performed six times under each of four swimming conditions: rested-solo, fatigued-solo, rested-group, and fatigued-group. He performed under each of these conditions twice after taking amphetamine, twice after taking secobarbital, and twice after taking placebo. The medication procedures will be described later.

After each performance the swimmer was asked to give a time-judgment for that trial. The actual performance times of the first (rested) and second (fatigued) swims were revealed to the subject after obtaining his time-judgment for the second swim. Two measures of judgment were derived from the relationship between performance time and the swimmer's time-judgment. The first, called judgment-error, is the unsigned, or absolute, difference between a subject's swimming time and his judgment of his swimming time. The second, called judgment-tendency, is the signed difference (algebraic sum) between swimming time and time-judgment and thus indicates whether a subject overvalued or undervalued his performance. A subject obtained a judgment-tendency score and a judgment-error score for each swim. A subject swam twice under each specific experimental condition (e. g., twice in groups, when fatigued, after taking secobarbital). The mean of a subject's two judgment-error scores for fatigued-group performances on placebo days was compared with the mean of his two judgment-error scores for that same swimming condition on secobarbital days to determine whether his judgment-error, under the fatigued-group condition, was greater after admin-

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of the organ is not badly damaged. If the renal injury is such that a laceration can be sutured, it is probable that it would have healed without surgical intervention.

Sometimes the patient with an injured kidney recovers from the immediate effects but from two to four weeks later develops symptoms and findings characteristic of a perinephritic abscess. Incision and drainage then becomes necessary.

TABLE 2.—*Surgical Treatment of Kidney Injuries*

Injury, Type	Injuries, Total	Nephrectomy	Conservative Surgical Treatment	Mortality
Contused	70	6	0	0
Fractured	21	0	3	1
Fragmented	6	5	0	0
Stabbing	7	0	3	0
Gun-shot	19	3	4	1
Total	126	14	10	2

In the past five years 126 patients with renal injuries were treated at the Los Angeles County Hospital (table 2). Seventy wounds were classified as renal contusions, 24 as fractures, 6 as fragmentations, 26 as penetrating wounds, 7 as due to stabbing, and 19 as gunshot wounds. Six of the 70 patients with contused kidneys were treated by nephrectomy for preexisting disease, including two with carcinoma of the kidney. The remaining 62 were treated with conservative measures (table 3). The end results were good in all of these. One patient with fragmentation of the kidney died on arrival at the hospital. The diagnosis was established at autopsy. The other six patients with fragmentation of the kidney were treated by early surgical intervention and nephrectomy, without mortality. Twenty-two of the patients with fractured kidney were treated by conservative management and only four required nephrectomy for renal complications. One patient in this group died of an associated head injury. Seven patients had stab wounds of the kidney. These were operated on immediately for associated intraperitoneal injuries. Four were managed conservatively, with one requiring nephrectomy 30 days after injury for uncontrolled bleeding. Nineteen patients were treated for gunshot wounds of the kidney. One patient died on arrival at the hospital. The remaining 18 were operated on immediately for associated injuries. Nephrectomy was performed in three patients for associated renal vessel injuries. In four, conservative surgical repair of the kidney was undertaken, with one subsequently requiring nephrectomy. In 11 there was no surgical entry into the retroperitoneal space. No sequelae or subsequent renal surgery was necessary in this group.

Summary

Patients with genitourinary injuries must be examined early and an accurate diagnosis of the extent of injury must be made to obtain the best results from treatment. Roentgenographic studies may be helpful in cases involving the lower tract and are essential in renal injury. More than one-half of straddle injuries can be treated without operation, but most posterior urethral and bladder injuries require it. The ureter should be repaired whenever it is injured, but more than 90% of renal injuries can be treated successfully without surgical intervention.

TABLE 3.—*Nonsurgical Treatment of Kidney Injuries**

Injury, Type	Injuries, Total	Died Before Treatment	Patients, No.	Delayed Operation, 2 Wk.*
Contusion	70	0	64	0
Fracture	24	0	21	4
Fragmentation	6	1	0	0
Stabbing	7	0	4	2†
Gunshot	19	1	11	0
Total	126	2	100	6

* There was no mortality associated with this series.
† 1 delayed healing, 1 nephrectomy.

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IDENTITY OF THE VIRUSES OF VARICELLA AND HERPES ZOSTER.—The evidence from laboratory studies now strongly supports the epidemiological evidence that chickenpox and zoster are due to the same virus. The results of antibody tests reported in the present series of papers, and particularly the earlier and greater antibody response observed in zoster cases, support the view that zoster is a second clinical manifestation of infection with varicella virus in persons whose immunity from the primary infection, whether clinical or subclinical, has waned. Virus from 21 cases of zoster and 22 cases of chickenpox was grown in tissue cultures of human fibroblasts or human amnion cells. The lesions produced were focal in character and infection spread by involvement of contiguous cells as described by Weller. The changes produced by virus from chickenpox vesicle fluid were indistinguishable from those produced by virus from zoster.—D. Taylor-Robinson, Chickenpox and Herpes Zoster: III. Tissue Culture Studies, *British Journal of Experimental Pathology,* December, 1959.

barbital days (since secobarbital was always taken in the second capsule). The difference might have been meaningful on amphetamine days, because amphetamine was always taken in the first capsule. However, analyses failed to reveal any clear-cut differences between the two-hour and the three-hour amphetamine days, with respect to either performance or judgment. Hence, in the analyses reported in this paper, the two-hour and three-hour data obtained from a subject under a given swimming condition and a given medicament were averaged.

The subjects were told this was a study of the effect of pep pills on performance. They were told they would sometimes get placebos, or blank pills, instead of the pep pills. No mention was made of the fact that secobarbital would sometimes be given. The subjects were told that the assignment of medicaments was random and that members of a particular group might, but might not, receive the same medicament on a given day.

Results

Since the styles and distances of the various subjects differed, their swimming times differed, ranging from about one minute to about three. The group means, with respect to performance and judgment times, were more strongly influenced by subjects swimming three minutes than by subjects swimming one. Analyses additional to those reported below were performed, expressing each subject's judgment-error and judgment-tendency scores as percentages of his mean placebo performance score, thus eliminating the differential contribution to mean effects due to differences in swimming time. These analyses yielded the same conclusions as did those based on the simpler and more direct measures reported in this paper.

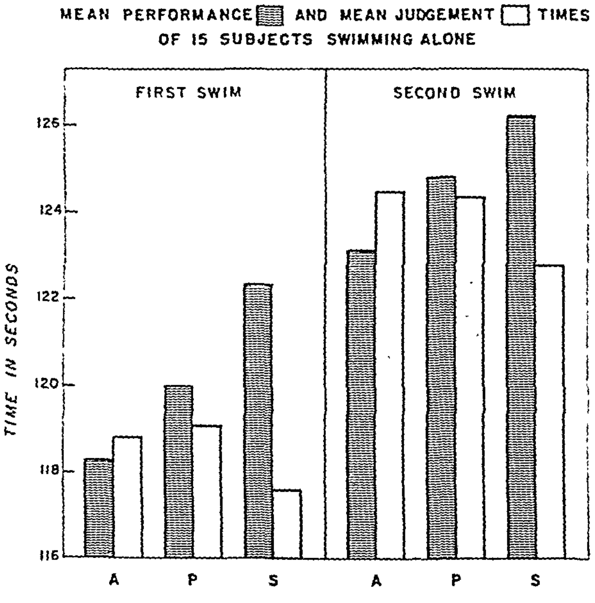

Fig. 3.—A=amphetamine sulfate; P=placebo; S=secobarbital sodium. Two-tailed probability values for effects of drugs on mean performance times are first swim, P-A=0.01, P-S=0.01; second swim, P-A=0.10, P-S=0.05. Two-tailed probability values for effects of drugs on mean judgment times are first swim, P-A=NS, P-S=0.10; second swim, P-A=NS, P-S=0.10.

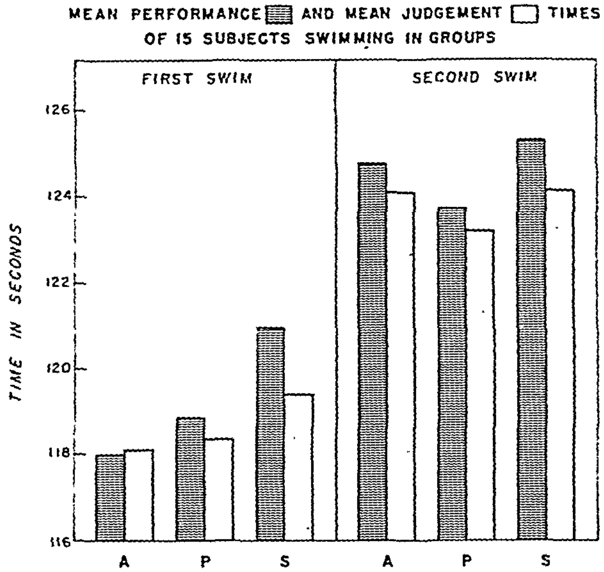

Fig. 4.—A=amphetamine sulfate; P=placebo; S=secobarbital sodium. Two-tailed probability values for effects of drugs on mean performance times are first swim, P-A=0.10, P-S=0.001; second swim, P-A=0.10, P-S=0.01. Two-tailed probability values for effects of drugs on mean judgment times are first swim, P-A=NS, P-S=0.05; second swim, P-A=NS, P-S=NS.

Judgment-Error.—Fig. 1 shows the mean judgment-error made by the 15 swimmers after taking amphetamine, secobarbital, and placebo—when swimming alone and rested, alone and fatigued, in groups when rested, and in groups when fatigued. The significance levels refer to differences between the mean placebo error (made under a specific swimming condition) and the mean error made after taking one of the two active drugs (under that same swimming condition).

Fig. 1 shows that the greatest judgment-error occurred when the subjects swam alone and rested after taking secobarbital. Under that condition the mean error was about four and one-half seconds, about three times that made by the subjects when they swam alone and rested after taking placebo. Under all four swimming conditions the mean judgment-error was greater after taking secobarbital than after taking placebo. The difference reached the 0.01 level of significance for both swim 1 and swim 2, when the subjects swam alone. When they swam in groups the difference reached the 0.05 level for swim 1 but was not significant for swim 2. (The mean judgment-error due to secobarbital was significantly greater on solo days than on group days. The differences reached the istration of secobarbital or placebo. This same general procedure was used in obtaining all comparisons reported below.

In addition to giving time-judgments a subject evaluated each performance by responding to a performance evaluation questionnaire containing 16 questions set up in this form: Did your legs feel: strong [ ], usual [ ], weak [ ]? The effects of the drugs on answers to these questions (subjective data) were examined in relation to the effects of the drugs on actual performance times (objective data) to obtain additional information regarding the influence of the drugs on judgment.

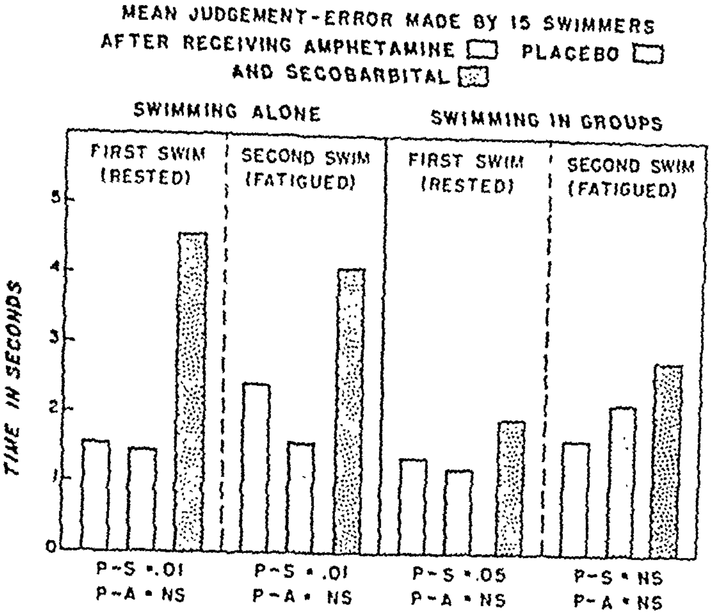

Fig. 1.—Judgment-error, based on unsigned difference between swimming time and judgment of swimming time. Probability values reported for comparisons between placebo and two active drugs were obtained by two-tailed correlated t test. NS means not significant at 0.10 level. Direct tests of difference between solo and group conditions are not reported in fig. 1, but they were carried out; results indicated that on secobarbital days difference was significant at 0.01 level for first swim and at 0.10 level for second. On amphetamine days difference was not significant for either swim.

The t test was used to evaluate the data concerning judgment-error, judgment-tendency, performance time, and judgment time, as shown in fig. 1-4. The binomial sign test [3] was used to evaluate the questionnaire data in the table. Throughout the text and figures of this report, and in the table, comparisons are said to be not significant if they fail to reach the 0.10 level as determined by a two-tailed test.

On two solo days each subject took secobarbital, 100 mg. per 70 kg. of body weight, on two he took amphetamine, 14 mg. per 70 kg., of body weight, and on two he took placebo. Similarly, on two group days each man took secobarbital, on two amphetamine, and on two placebo. Secobarbital sodium was used as a control medicament to prevent a subject from correctly assuming he had received a "pep pill" whenever he noticed unusual sensations. The drugs were administered orally and in a counterbalanced order which was unknown to the subjects or to the experimenter collecting the data.

Each day a subject took two capsules. The first was taken two hours before the first swimming trial on six days and three hours before it on the other six. The second capsule was always taken 55 minutes before the first trial. On "secobarbital days" the first capsule was always a placebo and the second contained secobarbital; on "amphetamine days" the first was amphetamine and the second a placebo; and on "placebo days" both were placebos. The double capsule technique was used so that a subject would have his first trial 55 minutes after taking the active medicament on secobarbital days and either two or three hours after it on amphetamine days; these were the periods of peak subjective effects found in our preliminary unpublished studies of the drugs. The difference between the two-hour and three-hour conditions probably had no meaning on placebo days (since both capsules were placebos) or on seco-

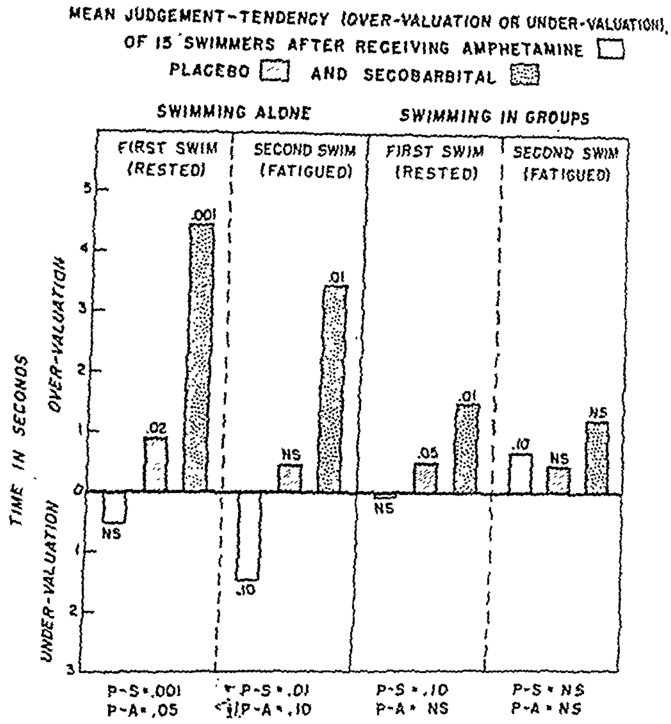

Fig. 2.—Judgment-tendency, based on signed difference (algebraic sum) between swimming time and judgment of swimming time. Each level of significance was obtained with two-tailed correlated t test. Those appearing immediately above or below bars refer to differences between zero and mean judgment-tendency under given drug and given swimming condition. Those appearing at bottom of figure refer to differences between mean placebo tendency and mean tendency under one of two active drugs. NS means not significant at 0.10 level. Direct tests of difference between solo and group conditions are not reported in fig. 2, but they were carried out; results indicated that on secobarbital days difference was significant at 0.001 level for first swim and at 0.02 level for second. On amphetamine days difference was not significant for first but was significant at 0.05 level for second swim.

on amphetamine than on placebo days (see table). These results indicate that the subjects failed to recognize the performance improvement produced by amphetamine; but the type of clear-cut and positive opposition between objective and subjective effects, observed with secobarbital under the solo condition, was not found with amphetamine.

Comment

The alterations in judgment due to secobarbital require little elaboration or explanation. The judgment-error data, judgment-tendency data, and performance-evaluation data all clearly demonstrate that a profound impairment of judgment was produced under the solo condition; most of the data suggest that a moderate impairment of judgment was produced when the subjects swam in groups of three.

The data concerning the effect of amphetamine on judgment are less clear in meaning. The judgment-error data revealed no greater error after amphetamine than after placebo (fig. 1). The judgment-tendency data showed significant differences between amphetamine and placebo under the solo condition, but these differences were due as much to the occurrence of overvaluation after placebo as to the occurrence of undervaluation after amphetamine (fig. 2). Both the performance-evaluation data (see table) and the mean judgment time data (fig. 3) indicated that, when swimming alone, the subjects thought their performances were about the same after amphetamine as after placebo; the fact, however, was that amphetamine significantly improved performance under the solo condition.

Additional evidence which would further clarify the meaning of the amphetamine data is sparse. Hauty and Payne,[18] with use of a different measure of judgment (by which the subject was required to estimate how well he would perform on a future trial rather than how well he had performed on a past trial), found that *d*-amphetamine (5 mg.) did not significantly influence the judgment of airmen studied with a psychomotor test. An earlier report by Davis [4] indicated that the antifatigue advantages of amphetamine might be counterbalanced by judgment impairment effects, but specific data demonstrating such judgment impairment were not presented.

Points for Emphasis.—Certain characteristics of the subjects and experimental situation, already mentioned, will be restated, because we believe they add to the dependability of the results obtained. The subjects were highly trained swimmers; each was accustomed to evaluating his performance and to estimating his speed. At the time of the investigation each subject was in midseason condition; thus, the variability of his performances was low. The judgments studied were not elicited in a contrived laboratory situation but were rather obtained in a real life situation, in which both swimming time and correctness of time-judgment appeared to be matters of importance to the subjects.

Differences Between Solo and Group Situations.—The effects of secobarbital and amphetamine on judgment-tendency and the effect of secobarbital on judgment-error were greater in the solo than in the group situation. Our data do not provide direct information concerning the reason for this difference. One can speculate, however, that when swimming

*Effects of Secobarbital Sodium, 100 Mg., and Amphetamine Sulfate, 14 Mg., per 70 Kg. of Body Weight, on Performance Evaluations of Fifteen Swimmers**

	Secobarbital vs. Placebo								Amphetamine vs. Placebo							
	Swimming Alone				Swimming in Groups				Swimming Alone				Swimming in Groups			
Questionnaire Item	S>P	S=P	P>S	p	S>P	S=P	P>S	p	A>P	A=P	P>A	p	A>P	A=P	P>A	p
First swim: rested																
Stroke felt good	11	4	0	0.01	9	3	3	NS	6	3	6	NS	8	5	2	NS
Swimming felt loose	10	5	0	0.01	5	6	4	NS	3	8	4	NS	6	7	2	NS
Start seemed fast	8	7	0	0.01	3	6	6	NS	8	4	3	NS	2	9	4	NS
Recovery was fast	5	5	5	NS	10	4	1	0.05	1	8	6	NS	2	5	8	NS
Swimming felt fast	10	3	2	0.05	9	1	5	NS	7	2	6	NS	9	2	4	NS
Swimming felt smooth	10	3	2	0.05	7	4	4	NS	4	5	6	NS	9	2	4	NS
Swimming seemed easy	9	5	1	0.05	10	1	4	NS	5	2	8	NS	7	6	2	NS
Made turns well	8	6	1	0.05	6	4	5	NS	5	7	3	NS	5	4	6	NS
"Revved up" before trial	4	9	2	NS	8	5	2	NS	9	4	2	0.10	9	2	4	NS
Did not have to drive self hard toward finish	9	4	2	0.10	8	4	3	NS	5	4	6	NS	4	7	4	NS
Second swim; fatigued																
Swimming felt smooth	8	7	0	0.01	6	3	6	NS	3	9	3	NS	4	3	8	NS
Recovery was fast	5	7	3	NS	7	5	3	NS	0	7	8	0.01	2	7	6	NS
Swimming seemed easy	7	6	2	NS	5	6	4	NS	5	5	5	NS	2	4	9	0.10
Start seemed fast	9	5	1	0.05	4	8	3	NS	4	6	5	NS	1	6	8	0.05
Made turns well	9	5	1	0.05	5	6	4	NS	7	5	3	NS	4	5	6	NS
Swimming felt fast	11	1	3	0.10	6	6	3	NS	5	4	6	NS	4	4	7	NS

* S>P: number of swimmers who reported more of a characteristic, listed at the left, after taking secobarbital than after taking placebo; S=P: number of subjects reporting no difference between secobarbital and placebo; P>S: number of subjects reporting more of a characteristic after placebo than after secobarbital. p: probability value associated with a two-tailed binomial sign test evaluation of S>P vs. P>S or of A>P vs. P>A. NS means the comparison failed to reach the 0.10 level of significance. Questionnaire items are not reported for the first swim if they were nonsignificant (NS) under all four conditions; the same is done for second swim comparisons.

0.01 and 0.10 levels for the first and second swims respectively.) None of the four differences between mean judgment-error after amphetamine and mean judgment-error after placebo was statistically significant.

Judgment-Tendency (Overvaluation and Undervaluation).—Fig. 2 shows the mean tendency of the 15 swimmers to overvalue or undervalue performance after administration of amphetamine, placebo, and secobarbital. A subject overvalued his performance if he thought he swam faster than was the actual case. Bars rising above the horizontal line indicate that the error of the subjects, considered as a group, was in the direction of overvaluation. Bars going below the line indicate undervaluation. Significance levels appearing immediately above or below the bars refer to the differences between zero and the mean judgment-tendency under a given drug and given swimming condition. Those appearing at the bottom of the figure refer to differences between mean placebo tendency and mean tendency under one of the two active drugs.

The subjects, considered as a group, overvalued after taking placebo, overvalued still more after secobarbital, and undervalued (in three of the four comparisons) after taking amphetamine. When the subjects swam alone, the difference between the placebo mean judgment-tendency and the secobarbital mean judgment-tendency reached the 0.001 level of significance for swim 1 and the 0.01 level for swim 2; when they swam in groups, the difference reached the 0.10 level of significance for swim 1 but was not significant for swim 2. The difference between the placebo and amphetamine judgment-tendencies was significant at the 0.05 level for swim 1 and the 0.10 level for swim 2, when the subjects swam alone; but when they swam in groups, neither comparison was significant.

The overvaluation due to secobarbital was significantly greater when the subjects swam alone than when they swam in groups ($p=0.001$ for swim 1 and 0.02 for swim 2). Also, the difference between the amphetamine mean judgment-tendency and the placebo mean judgment-tendency was greater when the subjects swam alone than when they swam in groups. The difference was not significant for swim 1 but reached the 0.05 level for swim 2.

Performance and Judgment.—Since the judgment-error data (fig. 1) and judgment-tendency data (fig. 2) are based on and derived from the relationship between performance time and judgment of time, it is of interest to examine the effects of the medicaments on each of these primary factors. Fig. 3 presents mean performance time and mean judgment time for the first and second swims under the solo condition. The subjects swam significantly slower after secobarbital than after placebo ($p=0.01$ for swim 1 and 0.05 for swim 2). Contrary to the actual impairment effect of secobarbital, the subjects, considered as a group, thought their performances were significantly faster after secobarbital than after placebo, on both swim 1 ($p=0.10$) and swim 2 ($p=0.10$).

When the subjects swam alone (fig. 3), amphetamine produced marked improvement on both swims ($p=0.01$ and 0.10 for first and second swims), but the subjects, considered as a group, thought that there was a slight impairment on the second swim and that the improvement on the first swim was much less than it actually was. Of the 15 swimmers, 13 performed better on amphetamine than on placebo days when swimming alone under rested conditions. Five of these 13 subjects judged their amphetamine performances to be poorer (instead of better) than their placebo performances and 6 undervalued the superiority of the amphetamine performances while only 2 overvalued it. When swimming alone under fatigued conditions 12 of the subjects performed better with amphetamine than with placebo. Seven of these subjects judged their amphetamine performances to be poorer (instead of better) than their placebo performances and three undervalued the extent of the superiority of the amphetamine performances while two overvalued it. Thus, under the solo condition, most of the subjects either failed to recognize the improvement in performance produced by amphetamine or, if they did recognize it, underestimated its extent.

Fig. 4 gives the mean performance time and mean judgment time when the subjects swam in groups of three. The effects of the drugs on mean judgment time parallel the effects of the drugs on mean performance time. As mean performance time goes up, mean judgment time goes up. Observe, however, that on both swims the differences among the mean judgment times were smaller than the differences among the mean performance times, indicating that although the subjects, considered as a group, correctly judged the direction of effect of both drugs, they underestimated the extent of effect of each drug.

Additional Subjective Data.—Responses to a 16-item questionnaire (designed to enable a subject to evaluate his performance) yielded results which are consistent, in general, with those reported above. Secobarbital significantly impaired performance (under both solo and group conditions), but the responses to the questionnaire indicated that most of the subjects failed to recognize the impairment produced by secobarbital under the group condition and thought secobarbital improved performance under the solo condition (see table).

Only four differences between amphetamine and placebo with respect to the 16-item questionnaire were statistically significant. The subjects reported feeling more "revved up" before the swim on amphetamine days but reported the start was slower, the swimming less easy, and the recovery slower conditions. He performed half of his rested and half of his fatigued trials swimming alone. He performed the remaining trials swimming with two other subjects. The data were collected in a "real-life" situation rather than a laboratory.

Comparisons between placebo and each of the two active drugs were made with respect to judgment-error (the unsigned difference between performance time and judgment time), judgment-tendency (the signed difference between performance time and judgment time), performance time, judgment time, and responses to a performance-evaluation questionnaire. Significance levels for the various comparisons were computed.

When the subjects swam alone, secobarbital significantly altered the mean judgment-tendency (the tendency being toward moderate overvaluation after placebo and extreme overvaluation after secobarbital), significantly increased the mean judgment-error, and caused the subjects to evaluate their performances as significantly better than usual, with respect to detailed aspects of performance, when in fact the performances were significantly slower. When the subjects swam in groups of three, after taking secobarbital, there was a tendency in the direction of a judgment distortion of the sort just mentioned but the effects were much less clear. When the subjects swam alone, amphetamine did not significantly alter the mean judgment-error but it did significantly alter the mean judgment-tendency (the tendency being to overvalue after placebo and to undervalue after amphetamine); the judgment time data (fig. 3) and questionnaire data (see table) indicated that, when swimming alone, most of the subjects either failed to recognize the improvement in performance produced by amphetamine or failed to appreciate its extent. When the subjects swam in groups, amphetamine did not produce significant effects on any of the measures of judgment. The effects of both active drugs on judgment-tendency, and the effects of secobarbital on judgment-error, were greater when the subjects swam alone than when they swam in groups of three.

It is concluded that secobarbital in the dose of 100 mg. per 70 kg. of body weight can, under certain circumstances, produce a profound distortion in judgment. A positive conclusion concerning the question whether amphetamine sulfate, 14 mg. per 70 kg. of body weight, is able to produce judgment distortion cannot be drawn from the present data. Since the drugs studied are in wide use, information concerning their effects on judgment is of interest, and the striking judgment distortion produced by the barbiturate is particularly important from the practical standpoint.

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alone the subject's time-judgment is probably based primarily on his "time sense" and whatever visual, cutaneous, and proprioceptive cues he obtains as he moves through the water. On the other hand, when swimming in a group (with team members whose usual speeds, in comparison with his own, are well known to him) his judgment is probably based on the additional cue of how he finishes in relation to his teammates. It is true that the degree to which this latter cue could be depended on by the swimmer was limited by the fact that he never knew which medicaments his teammates had received, or whether their performance times were altered. Nevertheless, we believe this additional cue in the group situation explains, in part, why the effects of the drugs on judgment were less in the group than in the solo situation. Whatever the explanation of the difference may be, the findings of principal interest are those obtained under the solo condition after administration of secobarbital, for these results show the extent to which the judgment of persons skilled in making the type of judgment studied can be distorted by such a drug.

Other Data Collected with Runners and Weight-throwers.—Judgment-error and judgment-tendency data were also collected on 25 runners and 13 weight-throwers, but most of the comparisons in these subsequent studies were not statistically significant. This group of 38 subjects did yield evidence of one sort, indicating a tendency to attribute a favorable effect to secobarbital when in fact none existed. After each performance, a subject was asked whether he thought the medicament he had taken that day helped or hurt his performance and if so, how. Twelve of the subjects gave more favorable reports on secobarbital than on placebo days, 23 reported no difference, and 3 gave more favorable reports on placebo than on secobarbital days. The actual fact was that 20 of the 38 subjects performed better on secobarbital than on placebo days and 18 performed worse. The experimental conditions maintained in the studies in which these 38 subjects participated were different, in certain respects, from those maintained in the investigation described above. First, the dose of secobarbital was only one-half that used in the study reported in this paper. Second, 16 of the 25 runners always ran under group conditions and, as shown above, the effects of secobarbital on the judgment of the swimmers were less in the group than in the solo situation and the effects of amphetamine were not significant in the group situation. Finally, the judgments of the 38 runners and weight-throwers were based on more dependable cues than were those of the swimmers. This was especially true of the weight-throwers; they actually observed the distance of each throw, and thus their after-performance estimates were a matter more of memory than of judgment. In the studies carried out, only one situation produced an indisputable example of judgment distortion, and that was the situation in which swimmers performed alone after taking 100 mg. of secobarbital.

Practical Implications

Under solo conditions secobarbital produced a judgment distortion of a profound sort; although performance was significantly impaired ($p=0.01$ for first swim and 0.05 for second swim), the subjects thought it was significantly improved ($p=0.10$ for both swims). Most of the data indicate that secobarbital produced a moderate judgment distortion when the swimmers performed in groups. We do not know whether this distortion was one of time-judgment only or whether it was of a more general nature; also, we do not know whether secobarbital would produce judgment distortion in a person who is accustomed to taking this drug. However, we think the findings described above have important practical implications because barbiturates are in widespread use[5] and because it is likely that many persons make decisions and judgments, and engage in potentially dangerous activities such as driving automobiles, after taking these drugs. The extent to which their decisions, judgments, and activities are influenced by the drugs, and the situational factors which alter such drug influences, are questions which have merited study[1] and require further study.

It is widely appreciated that alcohol can impair judgment and add to the hazard of normal activities. One can only wonder how many accidents occurring each year on the highway, in industry, in the home, and elsewhere are due in part to impairment produced by barbiturates, analeptics, tranquilizers, and other drugs given to ambulant patients. The widespread use of these medicaments by persons whose decisions, judgments, and behavior affect their own welfare and the welfare of others makes further quantitative assessment of the mental and behavioral effects of these agents a matter of practical importance.

Summary and Conclusions

Fifteen college swimmers, in midseason condition, swam 360 time trials after receiving secobarbital sodium, 100 mg. per 70 kg. of body weight, amphetamine sulfate, 14 mg. per 70 kg., or placebo on different occasions. The "double-blind" procedure was used. After each trial, a swimmer gave his time-judgment for that performance and completed a performance-evaluation questionnaire before being told his actual performance time. Each subject swam 12 trials under rested and 12 under fatigued

The minimum requirements to establish a diagnosis of sludging were that (1) aggregates must be seen in arterioles as well as venules and (2) all the erythrocytes must be in an aggregated form. Varying degrees of sludging beyond the minimum were (1) reduction in linear velocities of blood flow, (2) the presence of plugging of vessels, and (3) variable size of aggregates, with increasing numbers of large aggregates, i. e., over 20 cells per aggregate.

Eastham,[4] Bloch,[5] and Hirschboeck[6] have shown that there is a correlation of 80% or more between elevation of sedimentation rate and aggregation of red blood cells, both in vivo and in vitro. Gray[7] demonstrated a correlation between elevation of erythrocyte sedimentation rate and elevated plasma fibrinogen levels. In the present study, sedimentation rates and plasma fibrinogen levels were determined in all patients in whom sludging was diagnosed and were serially determined as an auxiliary guide to the evaluation of their sludging status. Fibrinogen levels were determined by a turbidometric method as proposed by Parfentjev and associates.[8]

Scherbel and associates[9] have shown that hydroxychloroquine (Plaquenil) sulfate has the fewest side-reactions of any antimalarial agent when used over long periods in the treatment of rheumatoid arthritis. Therefore, hydroxychloroquine sulfate was the antimalarial drug selected for this investigation. At present the initial dosage is 200 mg. four times a day for one week, followed by maintenance doses of 200 mg. three times a day.

Results

Forty-four human subjects with various vascular disease processes, in whom sludging had been noted in the bulbar conjunctiva, were treated with hydroxychloroquine sulfate, and their progress was followed serially with frequent observations and determinations of erythrocyte sedimentation rate and plasma fibrinogen levels.

Coronary Artery Disease.—Twenty-four of the patients had coronary artery disease, and 22 of these had had previous myocardial infarctions. One had a history of angina, with nondiagnostic electrocardiographic findings, and another had angina which was confirmed by the Master tolerance test. Five of the 24 patients were receiving anticoagulant therapy together with the antimalarial treatment. In two patients anticoagulant therapy was discontinued after institution of antimalarial therapy. Sixteen patients had no anticoagulant therapy at the time antimalarial therapy was started. Sixteen of the 24 patients had severe angina on exertion prior to antimalarial therapy.

Circulatory Changes: The circulatory changes noted in patients with coronary artery disease and sludging that was being treated with the antimalarial agent hydroxychloroquine sulfate were (1) elimination of plugging, (2) increased linear blood flow velocities, and (3) reduction in size of aggregates. At no time was complete desludging noted. The time required for appearance of these changes varied from two weeks to three months. Evaluation of patients with minimal sludging was practically impossible other than by determination of changes in sedimentation rate and plasma fibrinogen levels. Eight of the 24 patients with coronary artery disease showed minimal sludging. Two of them had normal sedimentation rates and fibrinogen levels and were dropped from the study because of the absence of clinical response, inadequate method of evaluation, and lack of cooperation. Two patients with extensive sludging who were taking a maintenance dose of 600 mg. of hydroxychloroquine sulfate showed no significant changes in circulation after two months. When their maintenance dose was increased to 800 mg. daily, plugging of vessels began to disappear.

Although there is an 80% correlation between sludging and elevation of sedimentation rates, there does not appear to be such a correlation between the extent of sludging and the degree of elevation of the sedimentation rate or the elevation of plasma fibrinogen levels.

Clinical Responses: Seven of the 16 patients with severe angina claimed to have a dramatic response within 72 hours after the onset of antimalarial therapy. These patients no longer complained of anginal pains except on severe exertion. Furthermore, after nine months of therapy none of these patients complained of an increased incidence of pain. Four of the 16 patients noted a significant drop in the incidence and duration of their anginal pains. These patients reported a 50 to 75% drop in their nitroglycerin requirements. Five patients showed no clinical response. There was no correlation between the time of relief of anginal pains and the time circulatory changes were noted. All of the previously mentioned patients had been unsuccessfully treated for their angina with drugs currently in use before an antimalarial agent was given.

Eighteen of the 22 patients with previous myocardial infarctions have strictly maintained their antimalarial therapy for nine months at the time of writing. None has had a recurrence of infarction while taking a maintenance dose of 600 mg. of hydroxychloroquine per day. Five of these patients had had more than one previous myocardial infarction.

Cerebrovascular Disease.—Eight patients with cerebrovascular disease and sludging were treated with hydroxychloroquine. Four of these patients were treated during the acute stage of a cerebrovascular accident. None was comatose, and all had gag reflexes. All experienced good recovery of functions. Changes in circulation that were noted included reduction of plugging, increased linear blood flow velocities, and reduction in sizes of ag-

USE OF ANTIMALARIAL DRUGS AS "DESLUDGING" AGENTS IN VASCULAR DISEASE PROCESSES

PRELIMINARY REPORT

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In the treatment of obstructive vascular diseases the use of drugs that inhibit sludging of erythrocytes is as logical as the use of anticoagulants. The antimalarial drug hydroxychloroquine sulfate is known to reduce the frequency of thrombotic and embolic phenomena in animals by a marked desludging action; it was administered to 44 human subjects in whom sludging had been noted in the bulbar conjunctiva. All had vascular diseases, and 22 had had previous myocardial infarctions. The initial dosage was 200 mg. four times a day for the first week; the maintenance dosage was 200 mg. thrice daily. Objective evidence of improved conjunctival circulation was obtained, and many patients, particularly those with angina pectoris and intermittent claudication, showed clinical evidence of improvement.

"Sludging" of blood is a nonspecific intravascular aggregation of erythrocytes. The presence of aggregates in the peripheral circulation tends to reduce linear flow rates of blood in small vessels. In addition, these aggregates can transiently plug small vessels. Aggregates can vary in size from 10 to 50 cells per clump, and the blood can be partially or completely aggregated.

Knisely and associates[1] were the first to describe sludging as part of a disease process when they observed it in monkeys infected with malaria. Since then Knisely and Bloch[2] have observed sludging in patients with trauma, infection, hypersensitivity phenomena, metabolic diseases, collagen diseases, neoplasia, and idiopathic phenomena.

Serial observations of peripheral circulatory changes were made on monkeys infected with malaria and then treated with antimalarial drugs. Knisely and Bloch[2] showed that, within 6 to 12 hours after administration of antimalarial agents to the animals, there was a marked reduction and even elimination of sludging. Linear blood flow velocities were markedly increased, and plugged vessels became unplugged. Comparison with untreated animals showed a marked reduction in thrombotic and embolic phenomena. In fact, untreated animals were "sludged" to death. The desludging produced by antimalarial agents was closely correlated with pronounced clinical improvement of the animal.

Inasmuch as desludging reduced embolic and thrombotic phenomena in animals infected with malaria as well as increasing peripheral circulation velocities, I wondered what the effect of desludging would be in various vascular disease processes which are complicated by sludging. Some of the disease processes considered are coronary artery disease, thrombophlebitis, cerebrovascular disease and accidents, arteriosclerosis obliterans, and bacterial endocarditis. If desludging reduces the incidence of thrombotic and embolic phenomena as well as increasing peripheral flow of blood, it should be possible to treat patients with the above-mentioned disease processes without fear of inducing bleeding, such as can occur with use of anticoagulants. Furthermore, it should be possible to relieve or improve anoxic pain by increasing the peripheral circulation.

Since antimalarial agents desludge blood in malaria, it is possible that they can desludge blood in other disease processes as well. Unpublished work of Knisely referred to by Bloch[3] revealed desludging in rheumatoid arthritis by the use of quinine. On the basis of this information it is believed that the effects of antimalarial agents should be studied in various vascular disease processes when sludging is present. This paper discusses preliminary results of such a study.

Materials and Method

Microscopic observation of the peripheral circulation was made on the bulbar conjunctiva of human subjects with a Greenough type of binocular stereoscopic microscope. The microscope was mounted on a vertical pillar which was attached to a horseshoe-shaped base. The base was placed under the patient's pillow and the microscope adjusted to visualize the conjunctival vessels. The light source was mounted on the microscope, and a variable transformer was used to control light intensity; a blue filter was used on the light. This is essentially the equipment used by Knisely and associates[1] who used a separate mounting for their light.

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The fact that there have been no recurrences of myocardial infarction in patients who have been maintained on antimalarial drug therapy for the past nine months is not yet significant; however, this is merely a preliminary report and the study will be continued for a long period. Since hydroxychloroquine sulfate has been proved safe over long periods, and since no bleeding results from its use, it is being given to ambulant patients. Recovery of function in patients with a cerebrovascular accident by means of therapeutic control studies is difficult to obtain; most will recover without treatment. Antimalarial therapy is much safer, however, than treatment with anticoagulants when no absolute differentiation can be made between thrombosis and hemorrhage. Determination of whether the antimalarial agents are effective in strokes will require their use in a much larger number of cases. The rapid response to use of antimalarial drugs by patients with thrombophlebitis suggests that they can be used together with other drugs, as part of the treatment.

The one patient with sickle-cell anemia who experienced relief of bone pain showed no change in her blood cells, although she experienced no recurrence of crisis or infection. It is possible that her improvement was related to a rapid venous return, with reduction in the amount of sickling by a time factor. Observation of her conjunctiva, after use of hydroxychloroquine sulfate as an antimalarial agent, revealed a marked increase in linear blood flow velocities in arterioles and venules. This report is meant to be preliminary and not conclusive. Further work is indicated, and, because of the unusual preliminary findings, it was felt advisable to report them at this time.

Summary and Conclusions

Therapy with the antimalarial drug hydroxychloroquine (Plaquenil) sulfate in patients with sludging and various vascular diseases has produced changes in circulation that can be seen in the bulbar conjunctiva, such as increased linear velocities of blood flow, reduction in the number of vessels plugged with aggregates, and reduction in sizes of aggregates. Because long-term use of hydroxychloroquine produces fewer side-effects than other antimalarial drugs, it was the drug of choice in this study. In no case was complete desludging observed. In nine months of follow-up observation no recurrence of myocardial infarction was noted in patients with previous myocardial infarctions who were given antimalarial therapy.

In about 40% of patients with postmyocardial infarction and angina, relief was obtained within 72 hours after institution of antimalarial therapy. An additional 25% of these patients observed, while on antimalarial therapy, a marked reduction in incidence and duration of anginal pain together with a 50 to 75% drop in their nitroglycerin requirements. One hundred per cent of the patients with sludging and intermittent claudication obtained a good clinical response to antimalarial therapy. One patient with sickle-cell anemia maintained a constant hemoglobin level, had clearance of her leg ulcers, and obtained relief from bone pain with antimalarial therapy.

The empirical results reported in this preliminary report indicate that desludging agents should be further and more extensively studied for their role in the treatment of vascular disease and in sickle-cell anemia.

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The Winthrop Laboratories, New York 1, furnished funds to build the microscope used to study circulation and also supplied Plaquenil, the hydroxychloroquine sulfate used in this study.

Drs. B. B. Teitelbaum, P. Kohn, M. H. Sobel, S. W. Kessler, D. Morrison, S. Friedman, S. Loeb, E. Adler, E. D. Schwartz, D. Lubin, H. Schweid, and W. J. Donaldy permitted use of their private patients as subjects for this study.

Drs. M. L. Siegel (Chief of Medicine at Mount Sinai Hospital) and Bennett Levine acted as consultants.

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gregates. One patient who had had a cerebrovascular accident six months earlier was given antimalarial therapy as a prophylactic measure; he too responded with changes in circulation.

Thrombophlebitis.—Eight patients with sludging and thrombophlebitis were treated with hydroxychloroquine, and two of the eight received no other medicaments. Seven of the eight patients showed clinical improvement within 48 hours. The eighth patient required 11 days to obtain reduction of induration and freedom from pain. In this instance, too, clinical responses preceded changes in circulation.

Intermittent Claudication.—Six patients with a history of intermittent claudication and an absence of both dorsalis pedis and posterior tibial artery pulsations were treated with hydroxychloroquine sulfate. All reported dramatic relief of pain within 72 hours. The maintenance dose varied between 600 and 800 mg. of hydroxychloroquine daily. When the patients occasionally had their dose reduced below 600 mg., recurrence of pains was reported. In two patients a return of pulses was noted, but no significant changes in oscillometric measurements were observed. The six patients with intermittent claudication responded with circulatory changes, such as increase in linear velocities of blood flow, decrease in size of aggregates, and diminution or elimination of plugging of vessels.

Sickle Cell Anemia.—One 20-year-old Negress with sickle-cell anemia and sludging has been receiving 600 mg. of hydroxychloroquine sulfate daily for eight months at the time of writing. In that time her tibial ulcers have completely cleared. She no longer complains of bone pain. She has had no infections since the institution of therapy, and her hemoglobin level remains between 7 and 8 Gm. per 100 cc. An increase in linear blood flow velocities and a reduction in the size of aggregates were noted in her bulbar conjunctiva after one month of therapy.

Side-Reactions or Complications.—Side-reactions have been minimal with use of hydroxychloroquine sulfate. Two patients had nausea, which was eliminated by reduction of the dose to 400 mg. every day for one week, followed by resumption of the 600-mg. dose. One patient developed pruritic erythema which cleared in 24 hours after withdrawal of the drug. Two patients developed unexplained eosinophilia, which subsided without withdrawal of the drug. Two patients had diarrhea, which was corrected by temporary reduction of the daily dose to 400 mg.

Comment

Reduction in plugging of vessels, reduction in size of the aggregates, and increase in linear-flow velocities of blood due to the use of antimalarial drugs, such as hydroxychloroquine, indicates that they may be desludging agents in disease processes other than malaria. One puzzling fact is that, in most cases, clinical responses preceded changes in circulation, and another that, within as little as 24 hours after withdrawal of the drug, symptoms in anginal patients and in patients with intermittent claudication recurred. It was also noted that reduction of the dose from 600 to 400 mg. daily brought on symptoms in many patients.

The rapidity of clinical action and the rapidity of exacerbation of symptoms suggests that some other factor, in addition to desludging, effects relief of symptoms. It may also be inferred that there is a rapid turnover of the drug, in spite of data showing heavy deposits in the liver and spleen.[10]

Steinbuch and Quentin[11] have shown that antimalarial agents (1) are adsorbed on the surface of red blood cells, (2) are capable of altering the shape of erythrocytes in vitro, and (3) are capable of flocculating solutions of stromal phospholipids of the red blood cells as well as solutions of lecithin and cephalin. Swank and Cullen[12] found that, when hamsters were fed a high-fat meal, sludging was present while the lipemia persisted. Goodman[13] showed that sodium palmitate was absorbed from serum and metabolized by human red blood cells. The fact that antimalarial agents alter the solubility or dispersibility of phospholipids and the fact that lipemia can produce sludging in vivo is highly suggestive that the mechanism of desludging by antimalarial drugs may be an alteration of the dispersing action of phospholipids in the plasma as well as on the red blood cell surfaces. If there is an effect on plasma phospholipids, one might explain the transient clinical effects of antimalarial agents by the fact that the phospholipid absorbed with each meal must be altered to inhibit sludging. Goodman[13] points out that, at high serum levels of palmitate, the adsorption of palmitate by the red blood cells is more than linear. Perhaps the sludging produced by lipemia can be related to the fat products adsorbed by the red blood cells.

Vascular disease processes such as angina, intermittent claudication, and even thrombophlebitis are difficult to evaluate clinically because of the tremendous individual variations in pain threshold and emotional response to disease processes. In this study, emphasis was placed on anginal patients who developed angina after myocardial infarction and who had not responded to therapy with other drugs, such as pentaerythrital (Peritrate) tetranitrate, tranquilizers, and heparin sodium, or to thyroid ablation. The fact that about 70% of the patients experienced some relief from anginal pains with antimalarial therapy by means of hydroxychloroquine, and that these responses persisted for nine months, to the time of writing, is of significance. Since the patients used for this study were private patients of various staff members at Mount Sinai Hospital, it was difficult to perform a double-blind experiment. However, a double-blind study has been initiated, although at the time of writing only four patients are included.

effects. Diphenhydramine (Benadryl), hydrochloride, however, which lacks the nitrogen linkage of the first group, reduces ureteral activity in frequency and amplitude. Promethazine (Fargan) hydrochloride was found to have a more inhibiting effect than diphenhydramine. Lapides,[4] in his work on the intact human ureter, found that the latter drug had no effect on normal ureteral activity.

Tetraethylammonium bromide produces a blockage of both the sympathetic and parasympathetic ganglions. It is thought to be a ureteral relaxant. This was confirmed by Lapides; however, he observed that this inhibition is the result of lowered urinary output from a decreased systolic blood pressure. He therefore postulated that ureteral peristaltic activity is not dependent on its autonomic nerve supply. Marshall,[5] on the other hand, used typhoid-paratyphoid (T. A. B.) vaccine to improve the degree of hydronephrosis in several patients so effectively that some appeared to have normal pyelograms. He then assumed that the drug has the effect of eliminating all inhibitory impulses, allowing relaxation and resumption of intrinsic muscular tone.

Neostigmine (Prostigmin) bromide has been used effectively in the expulsion of ureteral calculi by increasing ureteral peristalsis.[6] Lapides[4] had similar results in four of eight patients but concluded that this was due to the diuretic action of the drug and that, instead of any direct effect on the ureter, the change was due to the increased output of urine. Similarly, morphine produces an increase in ureteral contractions, and this fact has been confirmed by several clinical investigators.[7] With use of the same drug, Trattner[8] noted increase in ureteral activity in five patients, decrease in activity in two, and no change in two others. Lapides observed no change in ureteral activity with the use of morphine, and a similar effect was noted with the use of papaverine hydrochloride. Meperidine (Demerol) hydrochloride, which is considered to be a potent spasmolytic, has definite inhibitory effects on ureteral activity, but, again, there is a corresponding decrease in urinary output which may account for the apparent spasmolysis. Methantheline (Banthine) bromide, procaine, deproteinated pancreatic extract (Depropanex), and the nitrites have been used clinically in patients with renal colic with limited success. Recently valethamate bromide (Murel) has been reported to be effective; its mode of action is described as being anticholinergic, musculotropic, and ganglionoplegic.[9]

The benefit derived from the use of atropine in patients with symptoms of smooth muscle spasm on a pharmacological basis has long been recognized and used by members of the medical profession. The administration of atropine sulfate to patients with biliary and ureteral colic is quite common and sometimes effective. These beneficial attributes are appreciably reduced since the action of ingested atropine is short-lived. The oral administration of a dose of atropine sufficient to achieve therapeutic results also produces undesirable side-effects.[10]

Atropine tannate (Atratan), a new orally given medicament, has been found to be a remarkably effective antispasmodic and is unaccompanied by the usual side-effects associated with atropine. The use of this drug is based on a new chemical principle designated as Durabond. This relies on the function of a large molecular protocolloidal complex which, in itself not active, is the bonding action of atropine. A constantly maintained release of the therapeutic agent is assured despite variations in gastrointestinal motility or pH.

In this preliminary study 50 unselected patients with ureteral colic were observed. Patients with the diagnosis, on admission, of ureteral colic were immediately placed on therapy with orally given atropine tannate. They received a narcotic only if the therapy with atropine tannate did not successfully control the pain. This treatment was begun before the confirmation of the presence of a stone was made and was initiated in all patients who were seen with renal colic in spite of a history of either chills and fever, nausea and vomiting, urgency and frequency of urination, or hematuria. Even though some of these patients were later discovered to have other diseases, they have been included in this series in order that the full effect of the drug might be thoroughly evaluated for its efficiency in the relief of colic-like pain. Orally administered atropine tannate is available in tablets of 1 and 1.5 mg. Administration of 1 to 2 mg. of atropine tannate by mouth every four hours was satisfactory for most patients; several patients received 3 mg. initially and 3 mg. every four hours, however. Marked dilatation of the pupils was noted in the latter group of patients, but this did not appear to be a contraindication to continuing therapy with the drug. Four patients complained of side-effects, such as blurred vision, dizziness, and dryness of the mouth. In none of these, however, was it necessary to discontinue medication.

Report of Cases

The pertinent facts of these 50 cases are as follows. Forty patients in this series had ureterolithiasis. Thirty-nine of these patients were benefited by the use of orally given atropine tannate. One patient with a demonstrable ureteral calculus received no benefit whatsoever and received 100 mg. of meperidine every four hours until his calculus was removed with a stonebasket. Thirty-five of the remaining 39 patients required no administration of narcotics. The other four required narcotic therapy on one or two occasions. It was our impression that the amount of narcotic required and the frequency of its use was markedly reduced by the use of the orally administered atropine tannate.

URETERAL ANTISPASMODIC AGENTS

EXPERIENCES WITH ATROPINE TANNATE

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Findings are reported on use of long-acting atropine tannate in 50 unselected cases of ureteral colic. Patients with that diagnosis on admission were immediately given atropine tannate orally and received it every four hours thereafter. Thirty-nine of 40 patients with ureterolithiasis benefited from the atropine tannate. Thirty-five required no narcotics. Four required narcotics on one or two occasions. One of the 40 did not benefit from the drug. It is the authors' impression that the amount and frequency of narcotic required was markedly reduced by orally given atropine tannate. In 10 patients with no confirmation of ureterolithiasis there was no benefit. Initial investigation shows atropine tannate to be valuable in treating ureteral colic. There were side-effects but none so objectionable as to preclude its use.

It is our intention to present the available evidence regarding the effectiveness of drug therapy on ureteral activity, particularly in the alleviation of renal colic. A wide divergence of opinion exists in the literature regarding the use of related or identical medicaments, depending on the method of investigation and the interpretation of the results. This is not an unfamiliar circumstance.

In order to evaluate any ureteral antispasmodic, the normal physiology of the ureter must be understood. The ureter cannot be visualized simply as a tubal conduit of urine that is produced in the kidney and carried by hydrostatic pressure to the bladder. Rather one must realize that there is a dynamic action of the calyces, renal pelvis, and ureter which conduct the urine to the bladder by a synchronous sphincter action. A suction-like action of the calyces forces urine into the pelvis and at the same time sucks urine from the papilla through the ducts of Bollini. The pelvis in turn empties by a contraction of the infundibulum and a relaxation of the sphincter of the ureteropelvic junction. As the pelvis fills by relaxation a negative pressure, set up by contraction of the ureteropelvic junction, acts on the calyces to empty them. The pelvis is then in a phase of diastole and at the point of complete filling it undergoes systole or a detrusor action, emptying its contents into the ureter. The ureter is filled in thirds. The upper third discharges its urine into the middle third, where it remains until another rhythmical contraction propels it into the lower third and thence into the bladder. The latter action takes place as the upper third again empties into the middle third. The rate and amplitude of the rhythmical contractions depend generally on the amount of urine produced in the kidney. However, in partial or complete obstruction of the ureter a hyperperistalsis occurs in an attempt to overcome the obstacle. Colic results from the increasing back-pressure against the secreting portion of the kidney. Artificially obstructed ureters have been viewed by Benjamin under cineroentgenography, and he describes a cessation of peristalsis with early dilatation and tortuosity.[1] The physiopathological results after a complete obstruction are divided into three phases: (1) trauma; (2) muscular hypertrophy; and (3) atony, dilatation, and parenchymal destruction.[2] The end-results of these three stages are commonly referred to as hydronephrosis. A completely obstructed kidney is seen on intravenous urography to be a nonfunctioning kidney. It may continue to excrete in minute amounts, however, since the contrast medium opacifies the renal substance, giving a so-called nephrogram effect. This may be explained in part by absorption of fluid from the renal pelvis into the blood stream. The markedly concentrated urine that is drawn from the pelvis of an obstructed kidney is evidence to support this view. Although renal colic may persist for hours or days, a completely blocked kidney may later cease to give pain.

Action of Various Drugs on Ureter

A wide variety of reactions of the ureter to several drugs were obtained in laboratory animals, and these frequently are not confirmed in human beings. Frignani and Pezzuoli[3] found that synthetic antihistaminics have profound but opposite effects in dogs. Administration of tripelennamine (Pyribenzamine) hydrochloride will produce typical renal colic as will dimethyl-amino-ethyl benzylaniline (Antergan) and dimethyl-aminoethyl N-para-methoxybenzyl alpha-aminopyrine (Neo-antergan), which have similar chemical structures. Antazoline (Antistine), which differs slightly, produces similar

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ceptors be employed, whose training and teaching ability may be open to question; and over the proposals calling for a mere arbitrary doubling of the intern period. All these suggestions are primarily designed to solve the problem of the intern shortage. The welfare of the physician in training should determine the decision on the nature and length of this training period. Any change should be one that would make the most effective use of this precious period of training. The form of service recommended herein considers primarily the welfare of the intern. The advantageous features of the preceptorship can be incorporated into the recommended two-year program.

The real test of the quality of any service in an institution lies in having the intern on a service choose this service subsequently for his residency, on the basis of established superiority learned by actual contact with the service. Otherwise the decision is made by hearsay, without the knowledge acquired by personal experience. Competition for a candidate can stimulate all services to improve their training programs. A mixed service offers to graduates the opportunity to select an elective or a specialty on a sound basis, bolstered by personal experience. Only 37% of fourth-year students were "almost certain" of their choice of a specialty, and 9% had little confidence in their "preference" (Gee and Glaser, table A 40)[5]; yet, under present conditions, that choice is imposed when they select their internship.

Mixed Internship and Specialty Training

There is a consensus that a specialist should have a good basic background to encompass the peripheral fields before narrowing his effort and viewpoint specifically. This is imperative, if he is to bring his particular skills and special knowledge to bear, with full understanding, on the sick patient as a whole. There is nothing so tragic as the sight of a capable specialist acting like a layman in the presence of an acute emergency outside his field. The fulfillment of the Hippocratic oath demands that a physician have a minimum degree of practical general training to render emergency service. This ability often is not acquired in a straight internship followed by residency training in the specialty only. The type of service outlined here promises to make of the specialist a better physician in lieu of a superior technician, to increase his cooperation with and contribution to hospital and group practice. and to further his helpful participation in medical care in general and for the individual patient.

The elective feature in the proposed schedule of training will permit the graduate to embark on preparation for a specialty at the proper level of his own development and in proper relation to the other fields of medicine and to the patient. All these features warrant the full allowance of one year of internship and one year of special training toward the required period of preparation, without loss of time. The qualifying boards must concur in the inherent advantages to this end.

Internship and the Family Physician

Organized medicine and our medical educators stress the importance of general practitioners in the existing scheme of medical care. This is really lip service, for the specialties control our medical colleges and hospitals, and the student and intern are, in fact, exposed to the specialty viewpoint throughout. Yet 64% of all physicians are engaged in general practice, and 80% of all medical care is in the category of general practice. Indications are that this situation cannot be changed for many years. The present "paradox of holding medical students to higher standards and then accepting all degrees of compromise for subsequent training and practice" [15] must be corrected. A better allocation of training posts for both general practitioners and specialists is needed.[1a] The practitioner must be integrated into the scheme of medical care, and this requires good hospital training and provision for his participation in subsequent hospital practice. The American Association of General Practice is the only one of more than 100 national bodies that requires continued postgraduate study for continuation of membership.[3]

The two-year mixed service would properly prepare the general practitioner and help restore his former stature.[16] The recommended service would permit a more specific orientation to meet the needs of the general practitioner. He requires better training in geriatrics, psychosomatic medicine, allergy, dermatology, and neurology, which services are often better obtained in the outpatient clinic and home-care services. These services could be exploited by better organization, supervision, and administration, as foretold by Soma Weiss long ago. Training in observation and clinical judgment must not be surrendered to the laboratory and "diagnosis by gadget." [3] Every patient in the hospital should be examined by an intern in training for family practice, who would survey the whole patient before turning him over to special care. The intern should follow the patient's progress on all services. In this way, the criticism of the internship, "acquaintance with many specialties, but of one branch of medicine we catch only a glimpse, and that is general practice," can be avoided. This was the criticism of one-third of past interns in New York City.

There are two possible approaches to the adequate preparation of the physician for family practice. One is that of Dimond,[16] who advised broadening the training in existing residencies in internal medicine; this proposal has the distinct advantage of keeping medicine as the mainstay of the training and offers the basis for administrative identification and ultimate official credit control by the Board of Internal Medicine. The Committee on service does not extend to the learning process for the intern or to the maximum instruction each service can offer. Much of the art of medicine can be taught only by precept and example, but this is no excuse for failing to offer any instruction at all about matters which are equally difficult to teach by example or didactically." Too often the educational effort of an institution consists of a lecture program; the coordinator, if one exists, makes this his major contribution. His efforts are not concerned with the individual intern, his training, or his maturing practical experience. The educational gain from seminars, conferences, didactic lectures, and clinics is not on a par with that obtained by active participation and assumption of responsibility in medical care, in association with men of superior training and experience.

The wonder is that the internship has not been less successful. Its saving grace lies in the effective combination of stimulating teacher and avid pupil, which functions despite the lack of planning and organization. Without a stimulating, qualified staff interested in teaching, the hospital cannot hope to give a satisfactory internship. Approval of an institution for intern training now covers the essential facilities and material; it does not evaluate the more crucial educational process. One should look for a stimulating staff that offers a planned program as well as adequate facilities.

Most hospitals cannot provide an adequate training program and hence should employ for service needs recent graduates who have completed their intern and residency training. Of 6,970 hospitals only 1,590 are approved, and less than 15% are approved for intern training.[10] With present standards, this yields two vacancies for each graduate. We should admit frankly that few approved nonuniversity hospitals can approach a program recently outlined by Bauer.[11] Few can now offer the type of medical training which will yield "the ability to absorb and comprehend the medical knowledge that will be available tomorrow"[12]; yet this is imperative in the field of medicine, which is advancing so rapidly. This is the reason 50% of graduates seek out university hospitals for their internships. If university hospitals would undertake the two-year mixed service, such trained interns could be employed to improve service and training programs in community hospitals. The full teaching potential of a resident staff has not been utilized; this function needs formal appreciation and recognition. The faculties of our medical colleges must accept this important social responsibility and be concerned with the final training of the physician, the hospital and home care given to the patient, and medical care generally.

Only by offering realistic salaries and meaningful appointments on their staffs on completion of the intern's contract can such candidates be attracted to such institutions. Payment for the services of such house officers should be borne by the patient, the hospital, and the staff, since all will benefit from such better qualified personnel. Such a nucleus of well-trained interns and residents offer some of the benefits of full-time staffing in university or larger hospitals, from the standpoint of continuity of personal instruction for the rest of the house staff. They could assist in the instruction and assimilation of the foreign medical graduates, who, as of 1956-1957, have been holding one-third of the intern and resident positions in 1,242 hospitals and now occupy one-half in New York City and 65% in New Jersey. Others have stressed this aspect of the problem.[13] As Jennett[9] has put it, "However grand the names on the board in the vestibule, it is the House Staff that gives the hospital its real reputation."

Comparative Advantages

McKittrick[10] stressed that there is no single panacea for the internship. The existing situation offers two possibilities, (1) the liquidation of the internship or (2) its reorganization and improvement. If the attitude that opposes the mixed service per se is correct, then to be consistent we should abolish the internship completely, for the straight intern is, in effect, an assistant resident. We should completely transform our hospital training programs for graduates to the assistant resident level, and the fourth-year student clerkship would then become the equivalent of the internship.[14] In some colleges this has been prompted by the failure to attract an adequate number of interns, and "virtue has been made of necessity."[15] Others see harm for the college which weakens instruction in the last year and maintain that the internship "can be abandoned in name only" and that its abolition "will not solve anything, but create more problems."

Intern coverage for hospital needs should not be achieved at the expense of the student. The fourth year of instruction in our medical colleges needs strengthening, and the justification for the abandonment of the fourth year is questionable. Many believe that the transformation of the fourth year to release students "for service and 'training' in community hospitals" represents transmutation to a baser metal. The propriety of charging tuition for this year could be open to question. The clinical clerk, subject to call for required instruction and with an understandable detachment concerning his personal responsibility for the patient, cannot replace the intern. The clerkship, internship, and residency programs can be reciprocal and can supplement and strengthen each other and the educational program of an institution.[10] A recent survey indicated that 88.9% of interns thought the presence of a resident improved the value of their service, and 72.8% thought this also applied to the presence of clinical clerks.[7]

The proposed two-year mixed program presents practical advantages over the recommendation of Pullen,[14] which would impose on our medical colleges the difficult task of supervising internships in community hospitals; over the suggestion that pre-accomplished by inducing local community hospitals to improve their service and training programs by employing a nucleus of full-time interns and residents, who have completed their training recently, on their house staff. By thus minimizing the intern's financial hardship during the graduate training period, careers in medicine will not be limited to the wealthy and more and better candidates will again be attracted to the medical profession.

Institution of an adequate number of two-year mixed intern services with appealing educational programs is the best solution for the current shortage of interns and the serious eventuality that may follow the elimination of a large number of interns in many institutions by the American Medical Qualification Examination for foreign graduates.

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CLINICAL NOTES

SEVERE REACTION TO GRISEOFULVIN

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The successful systemic treatment of several types of superficial mycoses in humans by the oral administration of griseofulvin was recently described by Blank and Roth.[1]

Adverse reactions after the administration of this drug, in commonly used doses, have in general, been of slight import. Moreover, the maximum side-effects, including malaise, headache, mild gastrointestinal disturbances, evanescent leukopenia, and insignificant macular and papular eruptions, reportedly vanished promptly on discontinuation of the drug therapy.

The following report describes a severe generalized angioneurotic edema and persistent urticaria which occurred after griseofulvin therapy. This reaction was, in its clinical manifestations and in its response to therapy, an exact counterpart of the severe type of sensitivity reaction seen after the intramuscular administration of penicillin.

Report of a Case

A man aged 30 was under treatment for a typical hypertrophic lichen planus with intravenous injections of cyanocobalamin. On Dec. 16, 1958, he noted a flat, red, circinate, scaly eruption on the anterior chest wall. Scrapings from the lesion examined microscopically in potassium hydroxide preparation revealed many spores and mycelia. A typical Trichophyton rubrum fungus was obtained on culture.

Despite various types of local therapy and generalized ultraviolet irradiation, the circinate lesions continued to spread extensively on the anterior and lateral surfaces of the patient's chest and abdomen and sparsely on the back, buttocks, and upper parts of the arms. On Jan. 5, 1959, involvement of the toenails was noted for the first time and cultures of T. rubrum were obtained.

On March 9, 1959, the patient was placed in an experimental group receiving therapy with orally

Preparation for General Practice[8] of the American Medical Association recommends a new high-quality program for the family physician to meet the increasing need for the service of family practice. Three such experimental programs are to be instituted shortly (in July 1960 at the Indianapolis University and Kansas medical centers and at Baltimore City Hospital under the auspices of the Johns Hopkins faculty, if the necessary additional funds are obtained). This recalls the recently inaugurated program of special residencies in general practice; however, the attempt to establish special residencies for general practice does not seem to be the answer. Only 128 hospitals offer a total of 278 residencies and assistant residencies in general practice.[3] Only 65% of such approved residencies in general practice are filled at the time of writing. Only 404 physicians are in general-practice residencies, while 20,090 are in specialty residencies. A well-organized, mixed two-year internship could do what the general practice-residency program attempts to do, while promising wider acceptance with less dislocation of present programs and matching the recommendations of the Committee on Preparation for General Practice.[8] The one program herein suggested will simultaneously meet the needs of the rural physician and the general practitioner in larger communities, as well as those of future specialists.

There is a need to prepare the new physician, both general practitioner and specialist, better for group practice, which many agree is an effective means of rendering modern medical care for the patient by the doctor. The type of service recommended achieves a more cohesive hospital experience and better prepares the intern and specialist for cooperative hospital effort and group practice.

A pragmatic incidental advantage would be the solution of the serious problems of the current intern shortage and "being drowned in the case load" confronting medical education at all levels.[15] At present many hospitals have no incentive to provide good training programs, for it is obvious that they cannot now obtain native graduates as interns, no matter how intensive their efforts. In doubling the number of internships available, hospitals would be stimulated to institute stable plans for adequate training programs to attract candidates rather than to fill vacancies with aliens who have a language difficulty and often come from substandard schools; this has a deleterious effect on the morale of the entire staff of the hospital, and the patient and public health suffer too. Many of these foreign graduates obtain inadequate training, yet ultimately they often remain in the United States and enter the practice of medicine. Less than 10% return to their native lands from New York State. We are not fulfilling our responsibilities to these foreign visitors or to their countries of origin.[13]

The American Medical Qualification Examination can be expected to eliminate one-half of foreign interns, with larger proportions disqualfied in many hospitals. This may have a serious effect on hospital care if the supply of interns for hospitals is suddenly curtailed. Careful planning for this predicament that faces many institutions is imperative if the objectives of the qualification examination procedure are to be attained by making enforcement not wholly impractical. The suggested reorganization of the internship, with the formulation of a stimulating educational program by community hospitals employing graduate interns and residents already trained, may do just this.

The intern shortage cannot be solved by fiat or compulsion, but rather by making the recommended two-year intern service so attractive that few graduates will want to forego it. Recent studies again stress that, although marital status and other economic considerations may determine the nature of the service selected, it is the educational opportunity that determines the choice of a particular internship by candidates. A fundamental approach is necessary to improve the educational value of the internship and to include adequate remuneration. A directed effort is warranted, because the internship is the critical period for initiating responsible clinical training, and it is destined to play an increasingly important part in the preparation of the physician for the practice of medicine today and as it changes in the future.

Summary

A two-year mixed intern service system, as outlined, would be of advantage to the intern, the hospital, and the patient. Such a service, if well-organized, can offer the future physician practical experience under competent supervision and the opportunity for growth, with increasing personal responsibility. With proper orientation, the proposed training period will better qualify the family physician and enhance his prestige. It will also give a better basic background, without time loss, to those wishing to specialize or those seeking an academic career in teaching and research.

To attract interns, hospitals must offer a well-organized educational program as well as good facilities. Training of the intern must become a primary objective, and senior house officers should be used more formally and extensively. Among other steps that need to be taken to institute an effective two-year mixed service are the enlistment of the cooperation of medical teaching staffs, hospitals, specialty boards, and the U. S. Armed Services. This will result in better-trained physicians and in their better orientation toward group practice, with mutual benefits to all concerned.

Adequate remuneration must be provided for the tangibly valuable professional services rendered by the house staff of hospitals. This can be

SPECIAL ARTICLE

MORE INTERNS

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Because the number of approved internship positions in the United States is about twice the number of students graduating from the country's medical schools each year, many hospitals are facing an intern shortage. Similarly, only about one-half of all approved first-year residencies can be filled with U. S. graduates.[1] The importation of foreign graduates to fill more than 6,000 vacant jobs on each of these two levels of training has, in many instances, resulted in a disappointing experience for hospital officials and medical staffs, largely because of linguistic difficulties and discrepancies in standards of medical education.

Many hospitals affected by this shortage are facing the question whether to take steps toward increasing their popularity among U. S. graduates or to discontinue either their internship or residency programs, or both. If the latter choice is made, the private hospital virtually changes to a sanitarium, with house physicians taking care of patients under the private physicians' direction. A hospital that intends to retain its training function will find it necessary to analyze critically the reasons for its lack of success in the competition for qualified trainees and to study the factors which generally determine such success. Some of these factors that will be briefly considered in order of their probable importance are (1) quality of training programs for interns, (2) quality and number of residency programs, (3) compensation, and (4) tradition and reputation of a hospital.

Quality of Training Programs for Interns

The quality of an intern training program largely depends on two features, namely (1) supervision and active teaching and (2) availability of "service" patients. As regards item 1, bedside teaching remains the sine qua non of a clinical training program. Attending physicians must make regular and effective rounds with the house staff, spend the necessary amount of time on clinical examinations, review laboratory findings (including x-ray films) and discuss them, as well as write informative notes on each patient's chart. Rounds on "service" patients, in particular, should be held by physicians of proved ability, in accordance with an organized and dependable schedule. In the pediatric section, such rounds should be extended to include the nurseries for normal and premature infants as well as the study of contagious diseases. While on the surgical and obstetric services, the intern should participate not only in regular ward rounds but also in operative procedures and should be given ample opportunity to secure practical experience in preoperative and postoperative management. In obstetrics, particularly, it is essential that he carry out a number of deliveries well exceeding the minimum of 10 prescribed by the American Medical Association. Supervised and intensive experience with ambulant patients should be provided in the dispensary and in the emergency room.

At least one weekly clinical conference (grand rounds) and a regular (weekly, biweekly, or monthly) discharge conference (including review of all deaths) should be scheduled in each of these four departments, held in an auditorium, and attended by a representative number of staff members. These conferences should be on a sufficiently high level to be attractive to outside physicians. Other meetings, such as basic science seminars, radiologic and clinical-pathological conferences, and journal clubs, as well as organized research activities, have been well recognized as distinct assets in a clinical training program.

With regard to point 2, a sufficient number of "service" patients is necessary to enable the intern to "do things" rather than "watch things being done."[2] It is primarily on the "service" floors that the intern is enabled to initiate diagnostic and therapeutic measures and thereby develop self-confidence and independence of action. For obvious reasons, "service" patients are even more important in the surgical than in the medical specialties. (The problems created by the ever-decreasing number of indigent ward patients in the United States were amply discussed at the 54th Annual Congress on Medical Education and Licensure in Chicago on Feb. 10, 1958.[3]) Facilities for ready disposition of slowly convalescing and chronic patients should be available, especially where the number of "service" beds is limited. At any rate, "service" beds should be considered the nucleus of each department and should form individual units, physically separated from private beds.

Quality and Number of Residency Programs

A well-functioning and attractive internship program is hardly thinkable without a full-fledged residency program. The resident is the natural and, frequently, most effective teacher of the intern. Without specialty programs, it is often difficult to maintain an atmosphere of scientific interest; the ever-present need for correlation with the basic sciences becomes buried under the pressing daily routine caused by a large turnover of patients. The spark of academic inquiry which has been fanned administered griseofulvin. He received a dose of 500 mg. four times a day until March 16, after which the dose was reduced to 250 mg. five times daily until March 23, when treatment was stopped (after a total dosage of 25 Gm.) because of a shortage of griseofulvin. The itching ceased shortly after the beginning of therapy and the lesions began to regress. However, by April 14, 1959, three weeks after cessation of griseofulvin therapy, the lesions again began to spread, but without itching.

Four months after the interruption of treatment, griseofulvin (Fulvicin) became commercially available, and on July 21, 1959, the patient was placed on therapy with it, 250 mg. four times daily, which he took with good clinical result until Aug. 5, 1959 (total dose 14 Gm.). On this day he noted an itching eruption on the hips which he interpreted as mosquito bites. He took an additional 500 mg. of the drug the next day, despite extension and increased severity of the eruption.

When seen on Aug. 7, 1959, the patient had an extensive swelling of the orbital, zygomatous, ear, and lip areas; figured urticarial lesions over the entire trunk and extremities, with edema of the hands, wrists, feet, and ankles; and pain in the joints sufficient to produce almost complete limitation of motion.

Therapy for this reaction consisted of daily intravenous injections of 50 mg. of diphenhydramine (Benadryl) hydrochloride, plus 24 mg. of dexchlorpheniramine (Polaramine) maleate administered orally, for 5 days. This medication was followed by daily intramuscular injections of corticotropin (Acthar gel), 200 units, and methylprednisolone (Medrol), 4 mg. four times daily, until Aug. 16, 1959. Interruption of the antihistaminic or the steroid therapy was followed by recurrence of the urticarial and angioneurotic edema lesions. The latest recurrence, on Aug. 27, 1959, was finally controlled by the intramuscular injection of 40 units of corticotropin (Acthar gel). No further evidences of the reaction have been seen. However, by Sept. 10, 1959, new circinate fungous lesions were making their appearance on the anterior chest wall.

Comment

This patient had previously received penicillin in large doses for the treatment of an ear infection, without incident. A single dose (1 million I. U.) of procaine penicillin administered in December, 1958, resulted in some swelling of the arm around the site of the injection, but a similar dose given in the hip the next day produced no untoward reaction.

In the period before griseofulvin became commercially available, the patient tolerated administration of 25 Gm. of the drug without incident, and four months later he similarly tolerated 13 Gm. The beginning of the eruption was noted only after 14 Gm. had been ingested and the grave extension of the reaction after an additional 500 mg.

Whether the inadvertent interruption of the original griseofulvin therapy played a role in the later development of a sensitivity reaction is under consideration. It is a point to be seriously considered, however, in the light of existing recommendations for interrupted therapy in chronic nail infections.

Patch, scratch, intradermal, and passive antibod transfer investigations will be carried out in orde to elucidate this reaction more closely. There remains the unlikely possibility that this reactio represents a phenomenon of toxic overdosage—thi will be tested by readministration of the drug, beginning with small quantities.

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EYES INJURED DURING SOLAR ECLIPSE ON OCT. 2, 1959.—In this area, with an approximate population of 500,000, at least 15 cases of this condition, occurring mainly in children, have been seen, and, in the majority, permanent retinal damage and partial loss of central vision have resulted. Fortunately most appear to have used only one eye to look at the sun. A number were aware of the danger and used negatives or tinted glasses without being aware of the relative inefficiency of these filters. The unilaterality of these cases is apparently in contradistinction to the findings reported by Duke-Elder. If this area is representative, these findings suggest that, totally unnecessarily, at least 500 eyes have been permanently damaged over the country as a whole. Should not this be a stimulant to the very widest efforts at proper education of the public before the stars in their courses bring about the next solar obscuration? A notable feature of the present series was the apparent ignorance of the presumably educated and intelligent adult (headmaster, parent, etc.) of the danger of looking directly at any strong source of light. —M. J. Gilkes, D. G. MacPherson, A. H. Osmond, B. T. Thorne, and D. St. C. Roberts, Retinal Burns After Sun's Eclipse, Correspondence, *British Medical Journal*, Dec. 26, 1959.

are due to the effects of chronic depletion of body potassium on renal function and architecture. For descriptive purposes my associates and I have suggested that this lesion be called "kaliopenic nephropathy." The lesion consists of a vacuolar nephropathy mainly in the proximal tubules but sometimes extending into the distal tubules. In severe cases of primary aldosteronism there are scattered areas of tubular necrosis, with occasional spots of calcification. Various degrees of arteriolosclerosis have been observed. Much of the tubular lesion is reversible by potassium repletion, but functional recovery is likely to be slow although definite. In severe and long-standing cases of kaliopenic nephropathy a variable degree of irreversible damage may be present.

Kaliopenic nephropathy is a renal lesion of metabolic origin. In addition, however, a high incidence of pyelonephritis exists in patients with primary aldosteronism. This explains why this disease was called "potassium-losing nephritis" before its true pathological physiology became clear. There is some evidence to suggest that chronic kaliopenia decreases the resistance of the kidney to infection.

All these considerations point up the importance of early diagnosis and treatment before irreversible renal damage has occurred.

Postoperative Response in Primary Aldosteronism

Removal of the source of excess aldosterone production results in a dramatic disappearance of the entire syndrome in most cases. The usual response consists of a prompt internal rearrangement of electrolytes, urinary diuresis of sodium, a retention of variable quantities of potassium, and return of the carbon dioxide-combining power and blood pH to normal. These electrolyte and acid-base shifts are usually complete by the third postoperative week. All symptoms, including the polyuria and polydipsia, disappear abruptly.

In about two-thirds of the patients the blood pressure returns to normal within three months after operation and remains there indefinitely. In about one-fourth of the patients the blood pressure falls in the postoperative period to levels significantly lower than before operation but not to normal values. In a third group of patients, about 15%, the blood pressure may fall for several weeks or months and then gradually rise again to its preoperative level. It is significant that, in all cases (regardless of blood pressure response), the metabolic defect in electrolyte metabolism has been completely obliterated by the operation. Thus, hypertension, which was initially of steroid origin and was associated with a marked aberration of sodium and potassium metabolism, can return in the presence of normal metabolism of these electrolytes and in the presence of normal secretion of aldosterone, presumably on the basis of a secondary renal lesion produced in the course of chronic primary aldosteronism. Nevertheless, since kaliopenic nephropathy is at least partially reversible, and since the biochemical aberration disappears in all instances, one is obliged to advise operation in all these patients, even when severe renal damage can be demonstrated.

The occasional occurrence of two complications in the immediate postoperative period are worth mentioning. When severe renal damage is present, the decreased glomerular filtration rate which accompanies a lower blood pressure in the immediate postoperative state may intensify the degree of uremia. This has proved to be temporary and has disappeared as renal function improved over the ensuing months. More experience is needed to evaluate this completely. A second postoperative complication is the occasional presence of temporary or prolonged aldosteronopenia after removal of an aldosteroma. This situation is easily treated but must be recognized.

On the basis of the accumulating information it is my opinion that primary aldosteronism will prove to be a much more common disease than we think it is today.

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RESIDUAL PENICILLIN IN SYRINGES.—Contamination of syringes . . . is one of the most frequent hidden sources of penicillin exposure and one of great clinical importance. Either syringes or the water used in sterilizing solutions may account for this contamination. Coleman and Siegel called attention to this problem and emphasized that this transfer could be eliminated only after separation of the syringe parts, two or more washings, and autoclaving. A solution of penicillin boiled for more than 16 hours still produced a positive passive transfer test reaction on a site previously sensitized. Coleman and Siegel rightfully condemned the method of adding new sterilizing water as the old solution boils away. A much more preferable solution would be a complete and frequent change sterilizer water. Bierlein expressed doubt that the new high-pressure st used for the prevention of hepatitis is sufficient to inactivate
Nilsson and J. C. Sisson. Serious Reactions to Penicillin

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tients with proved cases of primary aldosteronism who, preoperatively, were completely asymptomatic but were known to be hypertensive. The condition in these patients was detected by routine testing of serum potassium levels in hypertensive persons. On the other hand, we have studied a patient who complained of some of the symptoms of primary aldosteronism, although initial biochemical study revealed normal levels of serum electrolytes and urinary aldosterone and no biochemical aberrations. Further study disclosed that hypopotassemia was demonstrable in about one-half of a long series of determinations of the fasting serum potassium level. Further, the urinary aldosterone level was elevated in some but not all the specimens tested. An 8-Gm. aldosteroma was removed, with an excellent clinical result. All gradations, from these cases that are merely difficult to detect to the full-blown disease have been observed. For mild cases newer testing procedures, such as the responses to potassium loading, administration of aldosterone antagonists, and compounds of the chlorothiazide-type are being studied, but definitive answers are not yet available.

Adrenals in Primary Aldosteronism

To date, a single, benign, well-encapsulated adrenal cortical adenoma has been observed in about 70% of the patients with primary aldosteronism. These have varied in weight from 0.5 to 87 Gm. The usual weight is 1 to 3 Gm. It is the small size of these tumors which needs to be emphasized. Failure to visualize them by the various roentgenographic techniques does not exclude their presence. Their small size also suggests the probability that some of the many small so-called nonfunctioning cortical adenomas which are seen at the autopsy table may, in fact, have been producing excessive amounts of aldosterone during life.

In 15% of the patients more than one adenoma was found in the removed adrenal gland at subsequent dissection. This suggests the possibility that, in some cases, the contralateral adrenal gland may also have contained small adenomas. Recurrent, adenomatous primary aldosteronism is a condition which, in some persons, will probably occur in the future after unilateral adrenalectomy for removal of one or more aldosterone-producing tumors.

Nine per cent of the patients had bilaterally enlarged adrenal glands due to cortical hyperplasia. The hyperplasia usually, although not invariably, has been nodular. The hyperplastic zone has usually resembled the fasciculi, but sometimes it has resembled the glomeruli alone or a combination of the two types of architecture. One interesting aspect of the patients with bilateral hyperplasia is their age. Most of these cases have occurred in children or young adults. The same type of lesion, however, has been found as late as the 5th decade of life. Total or subtotal adrenalectomy has produced amazingly rapid reversal of the disease. Polyuria and polydipsia, unresponsive to administration of vasopressin, in a child with hypertension is most likely to be primary aldosteronism. All cases of so-called nephrogenic diabetes insipidus should be reviewed with the possibility of primary aldosteronism in mind.

The remaining 6% of patients have shown adrenal glands of normal size. The architecture has appeared either normal or has shown focal nodular hyperplasia. The clinical picture has been typical, and large amounts of aldosterone have been found in the urine of such patients. Again, total or subtotal adrenalectomy has resulted in disappearance of the clinical and biochemical manifestations of primary aldosteronism. From this analysis it is clear that, in most cases of primary aldosteronism, the surgeon will be obliged to expose and inspect both adrenal glands before operating on either one. Furthermore, it will be necessary for the preoperative diagnosis to have sufficient support to eliminate hesitation in removing 90% of the adrenal tissue when tumor or hyperplasia fails to materialize at the time of adrenal exploration. Until future results can be evaluated, I believe that subtotal rather than total adrenalectomy is the procedure of choice in patients showing no tumor.

Undoubtedly, an occasional adrenal cortical carcinoma which produces exclusively an excess of aldosterone will occur. To date, those reported have shown, in addition, abnormally large quantities of urinary 17-hydroxycorticosteroids and 17-ketosteroids. Such combinations of excessive steroid excretion together with varied clinical manifestations are to be expected in patients with adrenal cancers. Although the major clinical expression in some of these cases may be that produced by excessive mineralocorticoid activity, they are by definition not cases of primary aldosteronism.

The importance of making a definitive preoperative differential diagnosis between primary aldosteronism and Cushing's syndrome is emphasized by the analysis of adrenal pathology given above. In primary aldosteronism the etiological factor is cortical adenoma (single or multiple) in 85% of cases, while diffuse bilateral hyperplasias is found in more than 50% of cases of Cushing's syndrome. Of the 9% of cases of primary aldosteronism associated with bilateral hyperplasia, 6% have shown diffuse cortical adenomatosis or diffuse nodular hyperplasia. Only 3% have shown the type of hyperplasia exhibited by over 50% of cases of Cushing's syndrome. Thus the informed surgeon can anticipate the type of pathology he is likely to encounter only after careful evaluation of the criteria on which the diagnosis has been based (see definition).

Kidneys in Primary Aldosteronism

The renal defect in tubular reabsorption of water which is resistent to administered vasopressin, as well as the inability to acidify the urine normally, and the assurance that funds would be available for those in financial need must be brought to attention of a large number of young Americans.

At the recent meeting of the House of Delegates in Dallas, this subject was considered at some length. The House approved the appointment of a committee to study a scholarship-loan plan. It would be modest in extent initially but would have a highly desirable effect on this complicated problem in America. It is hoped that the American Medical Association on authority of the House of Delegates and the Board of Trustees will act with a minimum of delay in implementing the recommendations of this recently appointed committee that are to be submitted at the Annual Session in June.

It is believed that at all times and unrelated to any action that might be taken by any official body, the physicians of America are duty bound to conduct a continuous campaign of education and recruitment in order to fulfill one of the precepts of the Hippocratic oath.

TRACHOMA

The report on trachoma in this issue (page 1577) from the United States Naval Medical Research Unit on Taiwan is believed to be one of the most important papers in the field of ophthalmology published in The Journal in several years. It further confirms the recent work of the Peiping, China, investigators in isolating the virus which is now believed to be the cause of trachoma. The trachoma vaccine described appears to be entirely safe, after having been injected into 450 human subjects without untoward reactions. Although a preliminary report, it provides some evidence for optimism from the standpoints of both prevention and treatment of a disease which has blinded human beings for centuries and from which millions of people still suffer throughout the world. This contribution also supports the deductions of other investigators. It is concluded that trachoma viruses are related to the psittacosis–lymphogranuloma venereum group. However, they clearly stand apart from other human viruses of that group. The authors found too, as many authors have, that the trachoma virus was sensitive to some antibiotics and other drugs, including penicillin, oxytetracycline, chloramphenicol, a sulfonamide, and a nitrofurazone compound.

The World Health Organization's Expert Committee on Trachoma has insisted that the proof that a virus under cultivation is the cause of trachoma should be the production of typical trachoma in human volunteers after sufficient passages in culture to eliminate by dilution any virus of the original inoculum. This requirement of the committee has been fully met, it is believed, by the investigators on Taiwan.

WISE MEN OF THE INCAS

We have written how it was ordered by the Incas that the statues be brought out at their feasts, and how they selected from the wisest among their men those who should tell what the life of their kings had been and how they had conducted themselves in the rule of their kingdoms, for the purpose I have stated. It should also be known that, aside from this, it was the custom among them, and a rule carefully observed, for each of them to choose during his reign three or four old men of their nation, skilled and gifted for that purpose, whom they ordered to recall all that had happened in the province during the time of their reign, whether prosperous or adverse, and to make and arrange songs so that thereby it might be known in the future what had taken place in the past.[1]

[1] These were in effect bards; this manner of "remembered history" appears in other, unrelated cultures. The Druids were court bards called ollamhs, their function not to guide and protect their king, "but merely to celebrate his temporal power." Richard Coeur de Lion employed a versificator regis to chant rhymed chronicles, epitaphs, and the like. The Welsh bards found, as did many other people, that "regular verse was a wonderful aid to memory and since vellum was prohibitively dear," writes Robert Graves in *The Crowning Privilege* (New York, 1956), "they recorded their chronicles, their teatises in geography, husbandry . . . in mnemonic rhyme" (page 98). Those numbered more than nine hundred such.

—The Incas of Pedro de Cieza de Leon, translated by H. de Onis, edited by V. W. von Hagen, Norman, University of Oklahoma Press, 1959, pages 172-173.

RUDOLPH VIRCHOW

Rudolf Virchow (1821-1902) of Berlin was the dean of pathologists for all time. His greatest service was to introduce the doctrine of cellular continuity of life into pathology. He did this very convincingly through his CELLULAR PATHOLOGY, a collection of lecture notes published in 1858 which stressed the importance of function in recognition of the blandness of a purely mechanistic outlook. In contrast to Rokitansky, who erred in his reasoning on the continuity of cells, Virchow correctly inferred that each cell must arise from a pre-existing cell, and, in fact, coined the famous aphorism expressing this view. Having laid such an unshakable foundation which for the first time transformed pathology into a unified science, Virchow soon became the world's leading pathologist.—J. Kevorkian, The Story of Dissection, New York, Philosophical Library, 1959.

PHYSICIANS FOR THE FUTURE

The supply of physicians in America for almost two decades after the great depression of 1929 increased steadily and provided a ratio of approximately 140 for each 100,000 persons. There appeared to be no critical shortage of professional personnel during this era, and those persons concerned with the planning for the number of physicians to be trained were relaxed and reassured. The rapidly rising birth rate since 1946, however, led to a proportionately greater increase in population than in the number of graduates of medical schools. The turning point occurred statistically in 1949. Even before the chronological peak occurred, concern over the adequacy of the then existing medical facilities was entertained. Since that time the ratio of physicians to population has diminished, without any immediate prediction of a reversal of this serious trend. According to the population statistician, there should be a 50% increase in the number of medical school graduates during the next decade and one-half to meet the growth in population if the ratio of physicians to population is to be maintained at the 1959 level.[1] Even this forecast may be insufficient since there exists no evidence to suggest that the physician of 1975 will be qualified to diagnose and treat as many patients per day or per year as at the present time. On the contrary, there are indications that, with the increasing complexity of diagnostic tools and because of the tremendous increase in the number of new and almost legendary pharmacologic agents, greater efforts of time and intellectual capacity will be required in the proper employment of the diagnostic tools and the therapeutic substances. Admittedly this phase of the subject is speculation, but it is safe to predict that the practice of medicine will become more rather than less complex for some time in the future.

Our apprehension in this discussion relates specifically to increasing the supply of skillfully trained medical graduates. There are two areas for exploration that are self-evident. The first is the expansion of existing medical school facilities or the building of new medical schools. The second is the recruitment of top-caliber college students for medical school. The expansion of existing medical school facilities would seem practical and logical on casual review. This is an erroneous conclusion if it were presumed that a large segment of the void between current enrollment and anticipated enrollment were to be corrected by this device. The first two years of basic science training in medical education requires laboratory space, pupil per pupil, and close supervision by qualified instructors, already short in supply in several of the basic disciplines. There is not a medical school in the United States that could increase the number of first-year students by 10 or at the maximum 20 without long-range planning if current standards of excellence are to be maintained. In a graduate school with predominant emphasis on lectures, such as the law school or the business school, a modest increase in the size of the entering class should not seriously disrupt either the quality of instruction or the skill of the end product. The medical school on the other hand is a peculiar educational enterprise. A trifling increase of the size of medical school classes is possible in selected instances without lowering the standards of the end-product, but if this proposal were pushed to any degree it would soon develop into a malignancy.

The construction of new medical schools is a corollary to the above proposal. Each of the several states in this country without a medical school has given serious thought to the creation of such a facility, partially or entirely with state funds. The immediate prospects for new medical schools in such states are not bright. Medical schools probably are the most expensive type of graduate schools to build and to maintain; meanwhile state legislatures appear to be more budget conscious than ever. There is yet one other aspect of the construction of a medical school sometimes overlooked. Schools should be planned only within the environs of a university, physically and spiritually. The proximity to a hospital is important for the provision of clinical material. The proximity to a university is equally important, academically and culturally.

If each of these two areas of exploration were exploited to the maximum and facilities were available to train a significantly larger number of medical students each year, whence comes the raw material for the finished product? Where do admissions committees of medical schools look for the receptive mind, the scholarly pupil, the dedicated spirit? Competition for the good student is a battle waged on a high intellectual plane between a number of disciplines. Engineers, chemists, physicists, and a myriad of other specialties distantly removed from the health-science field are as anxious to recruit from the house of intellect as is the medical faculty. One must dig deep into the early years of formal education to plant the seed and thereby create as favorable an impression as possible for the practice of medicine. It is not sufficient to wait until the student has completed one or two years of college. It is necessary to start a campaign of recruitment in adolescence. A crusade for enlightenment and mobilization should begin in the high schools and in the preparatory schools. The opportunities for a medical career, the intellectual satisfaction associated with the practice of medicine, the programs offered in forensic medicine. Instruction will be offered in such subjects as medical testimony, conduct of medical litigation, and techniques of presenting medical evidence in criminal cases. The first series of symposiums is scheduled for May 3 at the Law Center, entitled "The Hospital and the Law." Further symposiums to be scheduled later will include "Current Medical Legislation" and "Psychiatry and the Law."

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[1] Bane, F.: Physicians for a Growing America: Report of Surgeon General's Consultant Group on Medical Education, Bulletin 709, United States Department of Health, Education, and Welfare, October, 1959.

ILLINOIS

Northwestern Plans New Medical Curriculum.—Northwestern University Medical School, celebrating its centennial year, has planned a new medical school curriculum, it was announced March 21 by Dr. J. Roscoe Miller, Evanston, president of Northwestern, and Dr. Richard H. Young, dean of the Medical School. The revised curriculum, beginning in the fall of 1961, will be reduced from the traditional seven or eight years to six years for a group of 25 "talented" students accepted by Northwestern directly from high school. During two years of liberal arts work, they will take premedical courses in a more concentrated form and in graduate sequence. The program will also include a rearrangement of the medical and school curriculum for all students and the introduction of noncredit required courses in the humanities in seminar form at the medical school level. Northwestern reportedly is the first school in the country to receive support to put such a plan into operation. An initial grant of $257,177 from the Commonwealth Fund of New York will provide financial support for the first three years for the faculty members who will develop and present the new courses necessary to the program. The fund has also pledged $100,000 toward a new building to house special facilities for the new program and to provide additional clinical and research space for the medical school departments.

Chicago

Begin Construction of New Hospital.—On March 19, ground-breaking ceremonies were held for the New Holy Cross Hospital at 2700 W. 68th St. A service building providing heating, maintenance, and laundry facilities for the new structure has been completed and is serving the present hospital directly to the south of the new structure. Dr. Stephen Biezis, one of the first physicians appointed to the Holy Cross Hospital medical staff, was the principal speaker at the ceremonies. The hospital was originally opened in 1928. The number of beds is being increased from 143 to 325.

Study of Air Pollutants.—Atmospheric pollutants and their relationship to respiratory infections are being studied by scientists at Armour Research Foundation of Illinois Institute of Technology. Sponsored by the Air Pollution Medical Program of the U. S. Public Health Service, the program at present is concerned only with effects from gaseous pollutants, according to Richard Ehrlich, Ph.D., supervisor of biological research. The study is designed to determine whether or not pollutants, such as ozone, sulphur dioxide, nitrous oxides, and hydrocarbons commonly found in community atmosphere, affect the resistance to respiratory infections, such as pneumonia.

Seminar on Malpractice Liability.—A luncheon address by Mr. C. Joseph Stetler, director of the Legal and Social-Economic Division, American Medical Association, will be a feature of the Medical Malpractice Liability Seminar to be offered by the University of Chicago Downtown Center Wednesday, April 20. The one-day seminar, at the LaSalle Hotel, will present an "intensive grounding in the principles of medical liability" for physicians, dentists, and other nonlawyers. Instruction will be by attorneys experienced in medical malpractice problems, representing and advising both defense and prosecution, including insurance companies. Topics will include (1) liability of doctor to patient; (2) liability of doctor for acts of others; (3) malpractice insurance coverage; and (4) relation of medical and legal professions. For information, write the University of Chicago, University College, 64 E. Lake St., Chicago 1 (FI 6-8300).

MASSACHUSETTS

Harvard Biochemist Honored.—James D. Watson, Ph.D., associate professor of biochemistry, Harvard University, who determined the chemical structure of desoxyribonucleic acid (DNA), received the Eli Lilly & Company Award in Biological Chemistry at a general assembly of the American Chemical Society April 9. Dr. Watson collaborated with Dr. Francis H. C. Crick, of Cambridge University, England, in working to analyze DNA. The medalist became a senior research fellow at the California Institute of Technology in 1953 and in 1955 joined the Harvard faculty as an assistant professor of biochemistry. He was promoted to associate professor in 1958. In 1959, he and Dr. Crick were awarded the Warren Triennial Prize of Massachusetts General Hospital. The Lilly Award was established "to stimulate fundamental research in biological chemistry by young chemists working in the colleges and universities and other nonprofit institutions of the United States."

MINNESOTA

Dr. Moersch Retires.—Dr. Herman J. Moersch, senior consultant in medicine, former chairman of two sections of medicine and a member of the staff of the Mayo Clinic, Rochester, since 1926, retired from the active practice of medicine April 1 and

MEDICAL NEWS

CALIFORNIA

Dr. Motley Receives Alumni Award.—The University of Missouri Medical School Alumni Association Certificate of Merit was awarded to Dr. Hurley Lee Motley, professor of medicine and director of the cardiorespiratory laboratory, University of Southern California School of Medicine, Los Angeles, at the annual session of the Missouri State Medical Association March 13-16. Dr. Motley received an A.B. in 1930, an A.M. and a B.S. in 1932, and a Ph.D. in 1934 from the University of Missouri, graduating in medicine from Harvard Medical School, Boston, in 1936. He was director of the cardiorespiratory laboratory at the Jefferson Medical College in Philadelphia from 1947 to 1952.

COLORADO

Five Special Lectures.—The University of Colorado Medical Center, Denver, announced that on March 24 Dr. A. McGehee Harvey, professor of medicine, Johns Hopkins University School of Medicine, Baltimore, delivered the annual Sewall Lecture as the first of five lectures by guest speakers. On March 28, Dr. James A. Campbell, professor of medicine, University of Illinois College of Medicine, Chicago, spoke at the annual Alpha Omega Alpha Lecture and Honors Convocation. Dr. Campbell is national secretary of Alpha Omega Alpha. The annual Waring Lecture on April 11 will be presented by Dr. Wesley W. Spink, professor of medicine, University of Minnesota Medical School, Minneapolis, and first vice-president of the American College of Physicians. Dr. Hilary Koprowski, head, Wistar Institute, Philadelphia, will give the Phi Delta Epsilon Lecture April 21. The Lanier Memorial Lecture will be delivered May 10 by Dr. Russell H. Morgan, head, department of radiology, Johns Hopkins University School of Medicine, Baltimore. This annual lecture is in memory of Dr. Raymond R. Lanier, former head of the department of radiology of the Colorado University School of Medicine, who was fatally injured Nov. 24, 1958, in an automobile accident.

CONNECTICUT

Personal.—Dr. Stevens J. Martin, Hartford, was recently presented with the Horace Wells Award "in recognition of outstanding interest and achievement in the field of anesthesiology" by the Horace Wells Club of Connecticut, established 1895.—Dr. Charles M. Gratz, of Greenwich, has been invited by the Orthopedic Society of Mexico to deliver the orthopedic address of their annual meeting on April 16.

Yale Researcher Honored.—The 1960 Special Award of the Society of Cosmetic Chemists and its prize of $1,000 will be presented to Dr. Aaron B. Lerner, head, section of dermatology, Yale University School of Medicine, New Haven, "in recognition of his work on enzymes and hormones controlling skin pigmentation." He will be honored during the society's semiannual meeting May 12 at the Hotel Biltmore, New York City. Dr. Lerner, a pioneer in the study of melanin, reportedly was instrumental in the isolation of two melanocyte stimulating hormones from hog pituitaries. He was an assistant professor of dermatology at the University of Michigan Medical School from 1949 to 1952 and an associate professor at the University of Oregon Medical School from 1952 to 1955. In 1955 he was appointed associate professor of medicine and head of the section of dermatology at the Yale University School of Medicine and, in 1958, was promoted to the rank of professor.

DISTRICT OF COLUMBIA

New Institute of Forensic Medicine.—Dean Charles B. Nutting of George Washington University's National Law Center and Dean John Parks of the university's School of Medicine announced March 15 the establishment of the Institute of Forensic Medicine at the center, to be under the co-sponsorship of the Law Center and the School of Medicine. The institute will serve as a forum for the disciplines of law and medicine in areas where these professions are interrelated and where they vitally affect the public. Medicolegal problems of the individual and the community at the national and international level will fall within its scope. Dr. Murdock Head, assistant clinical professor of surgery and professorial lecturer in forensic medicine, was named chairman of the institute. Dr. Head is a graduate of the university's Law School and holds degrees also in dentistry and medicine. He is a practicing surgeon and a member of the Virginia and District of Columbia bars. In addition to classroom instruction and symposiums, institutes of several days' duration are contemplated, to meet needs of lawyers and physicians in practice as well as students enrolled in degree programs at the university. The university's medical and legal faculties will guide

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Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

Years"; a series of special lectures during April and May on scientific subjects; and a symposium on medical education and centennial dinner in the fall.

NORTH CAROLINA

Funds Support Professorships.—The Bowman Gray School of Medicine on March 19 received $500,000 for support of endowed professorships in the basic medical sciences. Funds for the professorships were provided by Mrs. Anne Reynolds Tate, of Pinehurst, and Mrs. Nathalie Bernard, of Winston-Salem. Mrs. Tate is a member of the board of visitors of the Bowman Gray School of Medicine and president of the board of trustees of the Blowing Rock Hospital. Mrs. Bernard was on the original committee that voted to establish the Bowman Gray School of Medicine of Wake Forest College in Winston-Salem. The Nathalie Bernard Lectureships at the school are named for her. Her benefactions to the school have included the gift of Graylyn Estate, valued at about 3 million dollars. The March 19 gift provides the first phase in the medical school's projected program of having at least one such endowed professorship for each of the school's 13 departments. The first three have been designated the William Neal Reynolds Professorship of Anatomy, the Odus M. Mull Professorship of Biochemistry, and the Gordon Gray Professorship of Physiology. Recommendations for individuals to fill these professorships will be made to the board of trustees of Wake Forest College when the selections have been determined. The executive council of the faculty has requested that the first three professorships be in the basic sciences—anatomy, physiology, and biochemistry.

PENNSYLVANIA

Scholarships Awarded for Postgraduate Study.—Five young scientists have been awarded Pennsylvania Plan scholarships for postgraduate study in the basic medical sciences at the University of Pennsylvania, Dr. Isidor S. Ravdin, vice-president for medical affairs at the university and chairman of the Pennsylvania Plan to Develop Scientists in Medical Research, announced. This is the third group of awards to be made under Pennsylvania's pioneer program of scholarship aid to "outstanding graduates" of medical, dental, and veterinary schools. The newly appointed scholars will start work under the program July 1. Object of the Pennsylvania Plan, inaugurated in January, 1958, is to "help relieve the shortage of basic science teachers and researchers" in the nation's medical, dental, and veterinary schools. Under the plan, scholars are awarded $7,500 a year for three years. This includes $6,000 for living expenses and $1,500 for laboratory equipment and supplies. Funds come from subscriptions of industrialists, businessmen, and other interested individuals.

Philadelphia

Dr. Lewis Honored.—Dr. Warren H. Lewis, an investigator and retired member at the Wistar Institute, was awarded the triennial Harrison Prize of $1,500 by the International Society of Cell Biology. A condition of the prize obligates the recipient to attend the forthcoming International Congress of Cell Biology, to be held Sept. 4-9 in Paris. The Harrison Prize, given every three years to recognize "outstanding research" in cell biology, commemorates Dr. Ross Granville Harrison, reportedly the first investigator to grow living cells outside the body. Dr. Lewis became a member of the Wistar Institute in 1940 while he was editor of "Gray's Anatomy." He was professor of physiological anatomy at Johns Hopkins University from 1913 to 1940, and was research associate at the Carnegie Institution of Washington from 1919 to 1940.

Affiliation of University and Hospital.—An agreement between the Presbyterian Hospital and the University of Pennsylvania for a teaching affiliation between the hospital and the university's schools of medicine was approved, in principle, according to a joint announcement made March 12 by the trustees of the hospital and university. The agreement in no way changes the independent status of the two institutions. Authority and responsibility for each will continue to rest solely with the respective boards of trustees. Details of organizational procedure involved in the affiliation agreement will be worked out by a joint committee of the hospital's medical staff and the faculties of the university's School of Medicine and Graduate School of Medicine. Under the agreement, the Presbyterian Hospital will offer its facilities for the purpose of undergraduate and graduate medical education at the university, and its staff will participate in the teaching program through arrangements to be worked out by the joint committee of medical staff and faculty. Procedures will be worked out whereby the hospital will maintain a research program under the auspices of its staff members and will receive assistance from the School of Medicine in obtaining grants for the conduct and support of the program. Physical facilities in both institutions will be utilized, whenever indicated and available, for the furtherance of the research program.

WASHINGTON

Surgery Meeting in Tacoma.—The 33rd annual meeting of the Tacoma Surgical Club, Tacoma, will be held May 7 at Jackson Hall, Tacoma General Hospital School of Nursing. The morning session will be devoted to the traditional anatomical dissections and demonstrations. Dr. Howard Ulfelder, clinical professor of gynecology, Harvard University, Boston, will present two papers: "Carcinoma of will soon assume the post of director of education and research for the American College of Chest Physicians. On April 1, 1938, he was named head of a section of medicine in the Mayo Clinic and on Jan. 1, 1948, was appointed chairman of two sections of medicine concerned primarily with the diseases of the chest. He became a senior consultant in medicine on Oct. 1, 1958. Dr. Moersch was president of the American College of Chest Physicians in 1956, and in the same year he was elected president of the staff of the Mayo Clinic. He is currently Vice-Chairman of the Section on Diseases of the Chest of the American Medical Association and will advance to chairman in June, 1960.

NEVADA

Meeting of Olympic Physicians.—The Nevada State Medical Association in cooperation with the Washoe County Medical Society and the Reno Surgical Society hosted visiting foreign and U. S. team physicians who participated in the VIII Winter Olympic Games immediately preceding the formal opening of that quadrennial event. Guests included Dr. Louis M. Orr, Orlando, Fla., President, and Dr. E. Vincent Askey, Los Angeles, President-Elect, American Medical Association, and Dr. T. Eric Reynolds, Oakland, Calif., president, California Medical Association, who received and dined with 26 team physicians from abroad and 44 U. S. team and ski patrol doctors, in addition to more than 80 Nevada doctors and their friends. The informal reception and dinner meeting was held at the Hidden Valley Country Club with Governor Grant Sawyer of Nevada welcoming the visitors. Dr. Per-Olov Astrand, Stockholm, Sweden, was spokesman for the visiting team physicians. Hosts for the evening were Drs. Ernest W. Mack, Reno, president, Nevada State Medical Association; John E. Palmer, Reno, president, Washoe County Medical Society; and Lowell J. Peterson, president, Reno Surgical Society.

NEW YORK

Rehabilitation Center in Rochester.—The general contract for construction of the Rehabilitation and Diagnostic Center at the University of Rochester Medical Center with a low bid of $1,011,000 was awarded recently. Total cost, including equipment and furnishings, is estimated at $1,494,000. Construction costs will be met by grants from the Ford Foundation, the Commonwealth Fund, federal sources, and with borrowed monies. The three-story building will be located on Crittenden Boulevard in front of the emergency department entrance to the University Medical Center. Work will begin in early April, and completion is expected by June, 1961. The Rehabilitation and Diagnostic Center will provide added facilities for the evaluation, care, and rehabilitation of the chronically ill. The new unit is part of the Greater University Program for the expansion of university facilities announced last fall. The ground level area of the new center will contain a waiting room, 20 private examining rooms, space for laboratory and limited x-ray facilities, areas for nursing personnel, a conference room for teaching, and a doctors' room. The second floor will contain the offices and conference rooms of the rehabilitation unit, with space allocated for the diagnosis and therapy of speech defects. The top floor will be used for physical restorative service and occupational therapy. A gymnasium for adults will contain equipment for physical therapy and special training. Vocational rehabilitation will be located in the basement of the new building.

New York City

Annual Lecture.—The second annual Louis Gross Memorial Lecture of the New York University–Bellevue Medical Center will be held April 25, 8:30 p. m., in the center's Alumni Hall, 550 First Ave. Guest speaker will be Dr. Bruce Cruickshank, associate director of the Mallory Institute of Pathology, Boston City Hospital. His topic will be "Localization of Tissue Antigens with the Fluorescent Antibody Technique."

British Lecturer.—Dr. Edward John Bowlby, deputy president, British Psychoanalytical Society, and director, department for children and parents, Tavistock Clinic, London, will deliver the Sandor Rado Lectures at the Columbia University Psychoanalytic Clinic for Training and Research April 29 and 30. The titles of his presentations will be "Anxiety and Grief in Infancy" and "Some Problems of Mourning."

Celebrate Centennial in Brooklyn.—The 100th anniversary of medical education in Brooklyn will be celebrated this spring and fall in a centennial program sponsored by the State University of New York Downstate Medical Center. The program opened March 30 with an academic convocation of scholars and doctors in the Center's Basic Sciences Building at 450 Clarkson Avenue, Brooklyn. Alvin C. Eurich, Ph.D., first president of the State University of New York and now vice-president of the Fund for the Advancement of Education, delivered the major address, entitled "A Look Ahead—The Second Century." Organized in 1860 as the College Division of the Long Island College Hospital, the medical school was chartered as the independent Long Island College of Medicine in 1930 and was merged with the State University of New York in 1950, becoming the first unit of the Downstate Medical Center. Other items in the centennial program will be the publication of a historical booklet, "Medical Education in Brooklyn—The First 100 may be borrowed for a small charge to cover handling. The publications include bibliographies. For information, write the Home Economics Research Center, School of Home Economics, University of Connecticut, Storrs, Conn.

Meeting of Head and Neck Surgeons.—The sixth annual meeting of the Society of Head and Neck Surgeons will be held April 17-19 at the Penn-Sheraton Hotel, Philadelphia, under the presidency of Dr. Arnold J. Kremen, Minneapolis. Thirty-five papers are scheduled for presentation on the program, the following of which will be presented by foreign authors:

The Incidence and Prevalence of Cancer of the Head and Neck, Dr. T. H. Crawford Barclay, Saskatchewan, Canada.
Tumors of the Maxilla and Jaw, Dr. Hector Rodriguez, Mexico City, Mexico.
A Study of the Use of Flap Procedures for Immediate Repair After Orbital and Orbito-Sinusal Exenterations for Malignant Tumors, Dr. Claude Chardot, Nancy, France.

The annual business meeting is planned for 4 p. m., April 18, with the society banquet to be held that evening. For information, write Dr. Harry W. Southwick, 30 N. Michigan Ave., Chicago 2, Secretary-Treasurer.

Medical Research Unit on Formosa.—In May, 1955, U. S. Naval Research Unit No. 2, originally organized at the Rockefeller Institute in New York City in 1942, was reestablished to conduct research on tropical diseases in Taipei, Taiwan. On Oct. 14, 1955, the Republic of China and the U. S. signed an agreement for medical research of area diseases by the U. S. Navy, for which a four-story building in the compound of National Taiwan University Hospital was leased. The Navy converted the building into a medical research institute with completely equipped laboratories, infectious disease wards, administrative offices, and storage and repair facilities. The commandant is Capt. Robert A. Phillips, M. C., U. S. N.

U.S. Naval Medical Research Unit No. 2 in Taipei, Taiwan (Formosa). A three-story wing is being expanded to double the present size.

Dr. J. Thomas Grayston, chief, Divisions of Microbiology and Epidemiology, injecting trachoma vaccine into a school child in Taichung.

The unit has 8 naval officers, 3 Civil Service scientists, 2 visiting professors on Office of Naval Research contracts, 10 enlisted men, 185 Chinese personnel, and 10 medical research fellows. Departments include administration, bacteriology, biochemistry, clinical investigation, entomology, epidemiology, immunology, parasitology, and virology.

In the research program, emphasis has been on viral and parasitic diseases. Studies on trachoma (see page 1577 of this issue) have been made with complete cooperation between laboratories, schools, public health administration, local officials, and the public.

In 1958, NAMRU-2 offered medical research fellowships to inhabitants of Taiwan, and the following year fellowships were offered to citizens of other countries in the Far East. Presently, besides three Chinese fellows there are two fellows from Korea, two from Thailand, one from the Philippines, and two from Japan who will arrive this month.

FOREIGN

Surgeons Meeting in Rome.—The 12th congress of the International College of Surgeons will be held May 15-18 at the Roman Palace of Receptions and Congresses (Palazzo dei Ricevimenti e dei Congressi), Rome, Italy. Sponsors of this year's congress are Giovanni Gronchi, president of the Republic of Italy, and Prof. Dr. Pietro Valdoni, head, surgical department, University of Rome. The congress will be made up of a general assembly and separate sections in the following specialties: anesthesiology, the Cervix" and "The Biomechanics of Pelvic Support." For information, write the Tacoma Surgical Club, 113 Medical Arts Building, Tacoma 2, Wash.

WEST VIRGINIA

Program to Honor Dr. Van Liere.—A special program will be presented at a meeting at the Medical Center in Morgantown on Thursday afternoon, May 12, honoring Dr. Edward J. Van Liere, who will soon retire as dean of the West Virginia University School of Medicine, a post he has held since 1935. The principal speakers on the program will be Dr. Carl J. Wiggers, of Cleveland Heights, Ohio, and David Bruce Dill, Ph.D., of the Army Medical Center, Maryland. Following the scientific program, Dean Van Liere's portrait will be unveiled and formal presentation made to the university. Following its acceptance by President Elvis J. Stahr Jr., there will be a reception honoring the dean. Following his retirement, Dean Van Liere will continue to serve on the faculty as professor of physiology.

GENERAL

Radiology Meeting in Boston.—The Eastern Radiological Conference will be held at the Sheraton Plaza Hotel, Boston, April 21-23, sponsored by the New England Roentgen Ray Society. The program will feature several symposiums from Harvard Medical School, Peter Bent Brigham Hospital, Massachusetts General Hospital, and Massachusetts Institute of Technology. Individual papers will also be included. A schedule of tours is arranged. Registration fee is $30 and includes the annual banquet, reception, and tours. For wives participating in the ladies' program the fee is $20. Radiologists and others interested may obtain information by writing Dr. John E. Gary, Secretary, New England Roentgen Ray Society, 1180 Beacon St., Brookline, Mass.

Cancer Conference in Denver.—The 14th annual Rocky Mountain Cancer Conference will be held in the new Denver Hilton Hotel, Denver, July 20-21. The regional cancer-control meeting is jointly sponsored each year by the Colorado Division of the American Cancer Society and the Colorado State Medical Society. Tentative program plans include a symposium, "Skin Cancer," the morning of July 20 and a symposium, "Thyroid Lumps," the following morning. Afternoon sessions on both days will be devoted to papers on cancer detection and treatment, by six physicians. Dr. E. Vincent Askey, Los Angeles, President-Elect, American Medical Association, and Dr. Warren H. Cole, of Chicago, president, American Cancer Society, will participate in the conference. Ten category I credits will be given by the American Academy of General Practice for attendance. For information, write the Rocky Mountain Cancer Conference, 835 Republic Building, Denver 2.

Congress on Artificial Internal Organs.—On April 10-11, the American Society for Artificial Internal Organs will meet at the Pick-Congress Hotel, Chicago. The program is arranged to include the following subjects:

Dialysis, Technical Aspects.
Design and Membrane Studies.
Hemodialysis.
Problems of By-Pass and Pumping Procedures.
Hypothermia and Cardiopulmonary Bypass.
Metabolic and Respiratory Studies During Extracorporeal Circulation.
Substitute and Accessory Hearts.
Artificial Heart Valves.
Cardiac Arrest.
Instrumentation.

Dr. Melvin M. Newman, Brooklyn, will present the presidential address at the dinner session April 10, 7 p. m. The business meeting is planned for April 11. For information, write Dr. Charles K. Kirby, 3400 Spruce St., Philadelphia 4.

Meeting of Harvey Cushing Society.—The 28th annual meeting of the Harvey Cushing Society will be held at the Fairmont Hotel, San Francisco, April 14-16. Four panel discussions are planned with the following titles: "The Treatment of Glioblastoma Multiforme and Medulloblastoma with Surgery and Irradiation," "The Surgical Aspects in Behavioural Neurophysiology," "Craniomaxillo-Facial Injuries," and "Occlusive Cerebrovascular Disease." Papers to be presented by invited authors include the following:

Subdural Hematomas in Children, Evaluation of Patients with Retained Subdural Membranes, Dr. Kenneth Shulman, New York City.
Subarachnoid Injection of Phenol in Pantopaque for Pain, Dr. Vernon H. Mark, Boston.
Repair of Skull Defects with Fetal Calf Bone, Dr. Robert S. Andre, Philadelphia.

The presidential address will be given April 15 by Dr. James L. Poppen, Boston, on "Neurosurgery in the Soviet Union." A banquet and dance are planned for April 14, beginning at 8 p. m. Exhibits are planned and ladies' activities are arranged. For information, write Dr. Edmund J. Morrissey, 450 Sutter St., San Francisco, Chairman.

Rehabilitation Aids for Handicapped Homemakers.—The School of Home Economics of the University of Connecticut, Storrs, announced the availability of films, publications, and exhibits for use in the vocational rehabilitation of handicapped homemakers. These aids are on work simplification in the area of child care for the physically handicapped and were developed by the school in cooperation with the Connecticut Team Approach Committee on Research, Demonstrations and Workshops Concerning Physically Handicapped Homemakers, and the Office of Vocational Rehabilitation, U. S. Department of Health, Education, and Welfare. Films

GOVERNMENT SERVICES

AIR FORCE

Society of Air Force Clinical Surgeons.—U. S. A. F. Hospital Travis will be host to the eighth Annual Symposium of the Society of Air Force Clinical Surgeons April 13-15, 1960.

NAVY

Russian Visitors.—Three Russian medical scientists visited the tissue bank at the National Naval Medical Center, Bethesda, Md., in February after attending the New York Academy of Science tissue transplantation conference. According to Prof. Mikhail M. Tarasov from the Skifosovsky Institute in Moscow, the work of the Center and particularly the work of the tissue bank is well known to scientists of the Soviet Union. Professor Tarasov is an exponent of the use for transfusion of blood from recently deceased persons who died of causes which would not prevent use of their blood for other human beings.

The other visiting Russians were Prof. Anastasy G. Lapchinsky, of Moscow's Institute of Experimental Surgical Apparatus and Instruments, where amputated limbs of animals have been rejoined to the same animal, and Dr. E. A. Zotikov of Moscow's Institute of Experimental Biology, who is concerned with the problem of the rejection of transplants of tissue grafted from one person to another. Escorting the visitors were Rear Adm. Bruce E. Bradley, M.C., commanding officer of the medical center, and Capt. George W. Hyatt, M.C., director of the U. S. Naval Medical School tissue bank.

A Century of Naval Medicine.—Presentation of a three-dimensional exhibit depicting a century of naval medicine, prepared by the United States Navy and the pharmaceutical firm of E. R. Squibb & Sons, was made to the Medical Museum of the Armed Forces Institute of Pathology. In addition to a panorama of naval medical accomplishments over the past century, the exhibit honors Dr. Edward Robinson Squibb who served as passed assistant surgeon in the U. S. Navy from 1847 to 1857. The exhibit will form the nucleus of a section of the museum devoted entirely to the contributions the Armed Forces have made to medicine.

PUBLIC HEALTH SERVICE

Training in Neuroradiology.—The first grants to support research training in neuroradiology were made by the National Institute of Neurological Disease and Blindness. Two grants, totaling $50,000, will be used to establish postgraduate programs for the study of advanced methods in the diagnosis and treatment of diseases of the nervous system through the application of radiant energy. The training will be made available at the Albert Einstein College of Medicine and the Neurological Institute of Columbia University. Both institutions will offer highly specialized training to qualified candidates who desire to prepare for investigative careers in this field. The training courses will be organized into two years of intensive study. The first year's work will emphasize such disciplines as neuroanatomy, neuropathology, neurosurgery, and clinical neurology. Training in the second year will focus on advanced techniques in neuroradiology.

The Institute is seeking other training centers where similar courses may be established in order to relieve the acute shortage of adequately trained neuroradiologists who can carry out research on neurological and sensory diseases.

Personal.—Dr. Dale C. Cameron, a career officer of the Public Health Service from 1937 to 1954 and director of the division of medical services of the Minnesota Department of Public Welfare since that time, has been recommissioned in the service and assigned to the National Institute of Mental Health, where he will be assigned to the training branch of the Institute. In addition, he will conduct a several months' study of mental health and mental hospital programs in a number of European countries. Later he will be detailed to St. Elizabeth's Hospital as assistant superintendent.——Dr. Harry F. Dowling, professor and head of the department of medicine at the University of Illinois College of Medicine, Chicago, and Dr. Francis S. Cheever, dean of the School of Medicine, University of Pittsburgh, Pittsburgh, were appointed to the National Advisory Allergy and Infectious Disease Council. On the recommendation of the council, the surgeon general awards grants to scientists in universities and other non-federal institutions for research on allergy and infectious diseases. The council also assists in providing guidance on broad research policies related to the programs of the National Institute of Allergy and Infectious Diseases.

FEDERAL AVIATION AGENCY

Personal.—Dr. George R. Steinkamp was designated acting chief of the review and records control branch in the office of the civil air surgeon of the Federal Aviation Agency. He will be responsible for supervising the agency's medical records, which total about 250,000 a year. Dr. Steinkamp was assigned to the FAA from the United States Air Force where he holds the rank of Lieutenant Colonel. Prior to his present assignment he was stationed at the U. S. Air Force School of Aviation Medicine, Brooks Air Force Base, San Antonio, Texas.

colon and rectum, heart, neurosurgery, obstetrics and gynecology, ophthalmology, orthopedics, otolaryngology, pediatric surgery, rehabilitation, sport injuries, chest, urology, and surgical nurses. Included in the general assembly will be four symposiums on the liver and intestines (portal hypertension, hepatic resection, biliary and gastrointestinal anastomosis, and ulcerous colitis). Other aspects of the congress will be scientific exhibits, medical movies, and commercial surgical and pharmaceutical exhibits. Official languages will be English, French, German, Italian, and Spanish, with simultaneous translations made at all sessions. After the congress, participants may travel to Tel Aviv to attend the Israel Section's Post-Congress International Conference, May 21-23, sponsored by the Israeli Ministry of Health, which will give special attention to the surgical and medical problems of young nations. For information, write the International College of Surgeons, 1516 Lake Shore Dr., Chicago 10.

CORRECTION

Piperazine Salts for Ascariasis.—In the letter from India entitled Piperazine Salts for Ascariasis, appearing in The Journal, Jan. 23, page 365, the reference should be *J. Indian M. A.* (33:317, 1959), and in line 13 of the second paragraph the percentage of positive results with the adipate should be 34 and not 84.

EXAMINATIONS AND LICENSURE

MEDICAL SPECIALTY BOARDS

American Board of Anesthesiology: *Written.* Various locations, June 24. Final date for filing application was January 10. *Oral.* Miami Beach, April 25-30. Applications already on file. Sec., Dr. Forrest E. Leffingwell, 217 Farmington Ave., Hartford 5, Conn.

American Board of Dermatology: *Written.* Various locations, June 5, 1961. Final date for filing application is March 1, 1961. *Oral.* Philadelphia, Oct. 13-16. Sec., Dr. Beatrice M. Kesten, One Haven Ave., New York 32, New York.

American Board of Internal Medicine: *Oral.* San Francisco, March 30-April 1; New York City, Nov. 14-17. Closing date for filing application: Jan. 2 and July 1. *Written.* Oct. 17. Closing date for filing application is May 1. Sec.-Treas., Dr. William A. Werrell, One West Main St., Madison 3, Wis.

American Board of Neurological Surgery: Examination given twice annually, in the spring and fall. St. Louis, April 10-12. In order to be eligible a candidate must have his application filed at least six months before the examination time. Sec., Dr. Donald D. Matson, 300 Longwood Ave., Boston, Mass.

American Board of Obstetrics and Gynecology: *Part II, Oral and Clinical.* Chicago, April 11-16. Final date for filing application was August 1. Applications for certification in Part I, new and reopened, and requests for re-examination in Part II are now being accepted. Deadline for receipt of applications is August 1, 1960. After July 1, 1962 a minimum of three years of approved progressive residency training will be required. Training by preceptorship will no longer be acceptable. The initiation of preceptorships will not be approved after July 1, 1960. Sec., Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

American Board of Ophthalmology: *Written.* Jan. 23, 1961. Deadline for filing applications is July 1. *Oral.* San Francisco, May 9-13; Chicago, Oct. 3-7. Sec., Dr. Merrill J. King, Box 236 Cape Cottage Branch, Portland, Maine.

American Board of Orthopaedic Surgery: *Part I,* Nashville, Denver and Philadelphia, Apr. 13-14. Deadline for receipt of applications was Nov. 30. *Oral and Written, Part II.* Miami Beach, Jan. 3-5, 1961. Final date for filing application is July 1. Sec., Dr. Sam W. Banks, 116 South Michigan Ave., Chicago 3.

American Board of Otolaryngology: *Oral,* Chicago, Oct. 3-6. Final date for filing application is April 1. Sec., Dr. Dean M. Lierle, University Hospitals, Iowa City.

American Board of Pathology: Memphis, April 21-23. Final date for filing application was March 7. *Examination in Forensic Pathology.* Memphis, April 22. Final date for filing application was March 7. Sec., Dr. Edward B. Smith, Indiana University Medical Center, 1100 W. Michigan St., Indianapolis 7.

American Board of Pediatrics: *Written.* New York City, January 1961. Final date for filing application is Dec. 1. Administrative Sec., Mrs. Eleanor J. Mitchell, Rosemont, Pa.

American Board of Physical Medicine and Rehabilitation: *Oral and Written.* New York, June 17-18. Sec., Dr. Earl C. Elkins, Mayo Clinic, Rochester, Minn.

American Board of Plastic Surgery: *Oral and Written.* Milwaukee, May 1960. Final date for filing application was January 1. Corresponding Secretary, Mrs. Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8, Mo.

American Board of Proctology: *Oral and Written, Parts I and III,* Philadelphia, Sept. 24. Final date for filing application is June 30. Sec., Dr. Stuart T. Ross, 520 Franklin Ave., Garden City, N. Y.

American Board of Psychiatry and Neurology: New York, New York, Dec. 12-13. *Child Psychiatry.* Chicago, April 25-26. Sec., Dr. David A. Boyd, Jr., 102-110 Second Ave., S.W., Rochester, Minn.

American Board of Radiology: *Examination.* Cincinnati, June 6-10; Dec. 5-9. Deadline for filing applications for the June examination was Jan. 1. Filing deadline for the December examination is July 1. A special examination in Nuclear Medicine (for those diplomates in Radiology or Therapeutic Radiology) will be offered provided there are sufficient applications. Sec., Dr. H. Dabney Kerr, Kahler Hotel Bldg., Rochester, Minn.

American Board of Surgery: *Oral Examinations (Part II):* Kansas City, Kans., May 16-17, and Los Angeles, May 19-20. Sec., Dr. John B. Flick, 1617 Pennsylvania Blvd., Philadelphia 3.

Board of Thoracic Surgery: *Oral.* May 1960. Final date for filing application was Dec. 1. Sec., Dr. Wm. M. Tuttle, 1151 Taylor Ave., Detroit 2.

American Board of Urology: *Written.* December. *Oral-Clinical.* Chicago, February 1961. Exec. Sec., Mrs. Ruby L. Griggs, 30 Westwood Road, Minneapolis 26.

Bucknam, Ralph Waldo Emerson Ⓜ Los Angeles; Medical School of Maine, Portland, 1895; member of the American Academy of General Practice; one of the founders of Hollywood Presbyterian Hospital, where he was a member of the staff and where he died Jan. 29, aged 87, of generalized arteriosclerosis and uremia.

Burdick, Austin Frederick, Grand Ledge, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1902; member of the American Academy of Ophthalmology and Otolaryngology; died Jan. 4, aged 81.

Burgess, Lyman Clawson, Derry, N. H.; Boston University School of Medicine, 1939; member of the American Academy of General Practice; veteran of World War II; association with U. S. Public Health Service terminated Nov. 8, 1943; died in the Veterans Administration Hospital in Manchester Jan. 22, aged 51.

Cahan, Jacob Morris Ⓜ Philadelphia; Jefferson Medical College of Philadelphia, 1915; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; on the faculty of his alma mater; served as medical supervisor and cardiologist, city board of public education; on the staff of the Jefferson Medical College Hospital; died Jan. 27, aged 71.

Campbell, Elliott Muse, Bellevue, Md.; George Washington University School of Medicine, Washington, D. C., 1919; veteran of World War I; died in the Memorial Hospital, Easton, Jan. 28, aged 65.

Cannon, Harold James Ⓜ Milwaukee; Marquette University School of Medicine, Milwaukee, 1921; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; associated with Misericordia Hospital and St. Joseph's Hospital, where he died Jan. 29, aged 65.

Champney, Richard Donald Ⓜ Milwaukee; Marquette University School of Medicine, Milwaukee, 1930; member of the American Academy of General Practice; veteran of World War II; on the staffs of the Deaconess Hospital and the Milwaukee Hospital, where he died Jan. 28, aged 54, of carcinoma of the bladder.

Chapin, David Raymond, Ardmore, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1900; died in the Bryn Mawr (Pa.) Hospital Jan. 25, aged 83.

Christensen, Hans Andrew, Brooklyn; Long Island College Hospital, Brooklyn, 1912; fellow of the American College of Surgeons; associated with Midwood Hospital and the Samaritan Hospital, where he died Jan. 25, aged 72, of cerebral thrombosis.

Clemens, William Joseph, Brooklyn; Fordham University School of Medicine, New York City, 1913; veteran of World War I; associated with the Hospital of the Holy Family, Bay Ridge Hospital, and St. Mary's Hospital; died Jan. 31, aged 70.

Collins, Marion Ⓜ Amsterdam, N. Y.; Woman's Medical College of Pennsylvania, Philadelphia, 1922; member of the American Psychiatric Association; died Jan. 24, aged 73.

Collins, Thomas A., Birmingham, Ala.; Birmingham Medical College, 1912; served on the staffs of the Children's Hospital and St. Vincent's Hospital, where he died Jan. 29, aged 71, of bleeding gastric ulcer.

Cooper, Clarence Melville Ⓜ Bellevue, Ohio; the Hahnemann Medical College and Hospital, Chicago, 1907; served on the staff of Bellevue Hospital, where he died Jan. 27, aged 78.

Costello, Clare George Ⓜ Kennewick, Wash.; St. Louis University School of Medicine, 1946; interned at the Providence Hospital in Seattle; formerly an officer in the medical corps, Army of the United States; died Jan. 24, aged 43, of burns received when his bed caught fire while he was smoking.

Daniel, George Preston Ⓜ Glen Daniel, W. Va.; University of Louisville (Ky.) Medical Department, 1893; died in a hospital at Beckley Jan. 20, aged 91.

Dayton, Spencer Thurman, Englewood, N. J.; Fordham University School of Medicine, New York City, 1919; died in the Englewood Hospital Jan. 7, aged 68.

Decker, Ernest Hamilton, Topeka, Kan.; St. Louis University School of Medicine, 1924; past-president of the Shawnee County Medical Society; veteran of World War I; served on the staff of the Atchison Topeka and Santa Fe Hospital; died Jan. 26, aged 64.

Diaz, Jose Maria, El Paso, Texas; Escuela de Medicina de Nuevo Leon, Monterrey, Mexico, 1891; died Jan. 26, aged 91.

Dobbins, James Matthew Ⓜ Long Island City, N. Y.; University of Buffalo School of Medicine, 1914; fellow of the American Academy of Pediatrics; past-president of the Queens County Medical Society; president of the medical board of St. John's Hospital; died Jan. 30, aged 67.

Downs, Thomas McKean, Bryn Mawr, Pa.; University of Pennsylvania School of Medicine, Philadelphia, 1921; specialist certified by the American Board of Surgery; veteran of World Wars I and II; member of the staffs of the Germantown Dispensary and Hospital in Philadelphia and the Bryn Mawr Hospital; died Jan. 29, aged 65.

DEATHS

Adlersberg, David Ⓜ New York City; Medizinische Fakultät der Universität, Vienna, Austria, 1921; specialist certified by the American Board of Internal Medicine; member of the American Gastro-Enterological Association and the Endocrine Society; fellow of the American College of Physicians; served as assistant clinical professor of medicine, Columbia University College of Physicians and Surgeons; associated with the Beth Israel, Mount Sinai, and Seton hospitals; died Jan. 10, aged 62.

Allen, Joseph Augustus Ⓜ New London, N. C.; University College of Medicine, Richmond, Va., 1901; died in Fayetteville Jan. 28, aged 90.

Atkins, Orman Hensley, Erin, Tenn.; Vanderbilt University College of Medicine, Nashville, 1910; died Jan. 28, aged 75.

Babcock, Claude Elliott Ⓜ Keene, Calif.; College of Medical Evangelists, Loma Linda and Los Angeles, 1934; interned at the Maryland General Hospital in Baltimore, where he served a residency; served a residency at the Los Angeles County Hospital in Los Angeles and the Olive View Sanatorium in Olive View; certified by the National Board of Medical Examiners; member of the American College of Chest Physicians and the American Trudeau Society; associated with the Stony Brook Retreat; died in Los Angeles in January, aged 52.

Baer, Walter Ⓜ St. Paul; Albert-Ludwigs-Universität Medizinische Fakultät, Freiburg, Baden, Germany, 1921; interned at the Charles T. Miller Hospital; associated with the St. Luke's, St. Joseph's, and the Charles T. Miller hospitals; died Jan. 16, aged 61.

Bald, Arno Albert, San Diego, Calif.; University of Nebraska College of Medicine, Omaha, 1911; served on the school board of Platte Center, Neb.; died in January, aged 73.

Baldwin, Arthur Mann Ⓜ East Palestine, Ohio; University of Pittsburgh School of Medicine, 1926; died in Youngstown Jan. 19, aged 59.

Ballenger, Oscar Leonidas, Chicago Heights, Ill.; Jenner Medical College, Chicago, 1904; died in St. James Hospital Jan. 21, aged 84.

Barnes, Richard Dee, La Canada, Calif.; College of Medical Evangelists, Loma Linda and Los Angeles, 1959; interned at the Los Angeles County General Hospital; died Jan. 30, aged 28.

Berg, Evelyn Victoria, Great Neck, N. Y.; Tufts College Medical School, Boston, 1931; interned at the Philadelphia General Hospital; certified by the National Board of Medical Examiners; associated with the Parsons Hospital in Flushing and the North Shore Hospital in Manhasset; died Jan. 25, aged 53.

Bernstein, Charles Ⓜ Brooklyn; Long Island College of Medicine, Brooklyn, 1934; interned at the Coney Island Hospital in Brooklyn; veteran of World War II; died Nov. 18, aged 58, of a heart attack.

Bertucci, Emile Augustus Ⓜ New Orleans; Medical Department of Tulane University of Louisiana, New Orleans, 1912; formerly on the faculty of his alma mater; for many years assistant medical director for public schools in New Orleans; died Jan. 21, aged 71, of carcinoma of the transverse colon with metatastic lesions of liver.

Bilmes, Harry M., New York City; Universite de Montpellier Faculte de Medecine, France, 1916; died in the Hospital for Joint Diseases Jan. 24, aged 74, of pulmonary embolus.

Bitting, Numa Duncan Ⓜ Durham, N. C.; Jefferson Medical College of Philadelphia, 1907; also a pharmacist; fellow of the American College of Surgeons; served on the staff of the Watts Hospital, where he died Jan. 18, aged 82.

Black, Fred Wallace, Lewistown, Pa.; Medico-Chirurgical College of Philadelphia, 1907; veteran of World War I; received many decorations, including the French Legion of Honor; founder of the F. W. Black Hospital; died Jan. 29, aged 79.

Boyd, Granberry Davis Jr. Ⓜ San Antonio, Texas; Baylor University College of Medicine, Dallas, 1928; member of the American Academy of General Practice; served as health officer of Bexar County and as coroner; veteran of World War II; died Jan. 19, aged 58.

Brown, Glynne Ⓜ Tyler, Texas; University of Virginia School of Medicine, Charlottesville, 1925; associated with the Mother Frances and Medical Center hospitals; died Jan. 19, aged 58.

Brown, Harvey Lee, Laurel, Miss.; Leonard Medical School, Raleigh, N. C., 1905; veteran of World War I; died Jan. 12, aged 83.

Brown, Maurice Ⓜ Philadelphia; Jefferson Medical College of Philadelphia, 1909; died in the Memorial Hospital, Savannah, Ga., Jan. 7, aged 72, of injuries received in an automobile accident.

Ⓜ Indicates Member of the American Medical Association.

Ivey, Donnell Ragan, Monticello, Ind.; Central College of Physicians and Surgeons, Indianapolis, 1904; president of the Royal Center Community State Bank; died in the White County Memorial Hospital Jan. 17, aged 81.

Jackson, Marshall Alan, Little Rock, Ark.; University of Arkansas School of Medicine, Little Rock, 1959; died Jan. 20, aged 31.

Joffe, Sophia Arlene Ⓜ West Chicago, Ill.; Chicago Medical School, 1949; interned at Macon (Ga.) Hospital; served a residency at the Elgin (Ill.) State Hospital; died Feb. 7, aged 55.

Kaminski, Theodore John Ⓜ Cleveland; Eclectic Medical Institute, Cincinnati, 1927; on the staff of *the Huron Road Hospital in East* Cleveland; *died* in Independence, Ohio, Jan. 24, aged 66.

Keck, Herman, Cincinnati; University of Cincinnati College of Medicine, 1922; died in the Good Samaritan Hospital Jan. 24, aged 61.

Keitz, Emile Sylvestre, New Orleans; Medical Department of Tulane University of Louisiana, New Orleans, 1906; associated with the Eye, Ear, Nose and Throat Hospital; died Jan. 11, aged 78, of congestive heart failure.

Kiblinger, Ada Christine Schwing Ⓜ New Orleans; Illinois Medical College, Chicago, 1907; died Oct. 31, aged 83, of cerebrovascular accident.

Kite, John Edgar Jr. Ⓜ Bullsgap, Tenn.; University of Tennessee College of Medicine, Memphis, 1935; interned at Stamford (Conn.) Hospital; served a residency at the South Highlands Infirmary in Birmingham, Ala.; a company surgeon for the Southern Railway System; died in Greeneville Jan. 29, aged 46.

Kjelland, Andrew Arthur Ⓜ Hatton, N. D.; University of Minnesota College of Medicine and Surgery, Minneapolis, 1910; on the staff of the Northwood (N. D.) Deaconess Hospital; past-president of the Traill–Steele District Medical Society; died Jan. 18, aged 79.

Kremer, David Nathaniel Ⓜ Philadelphia; University of Pennsylvania School of Medicine, Philadelphia, 1911; served on the faculty of his alma mater; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; associated with the Philadelphia General Hospital and the Doctors' Hospital; died Jan. 29, aged 69.

Latte, Julie Mathilde, New York City; Ludwig–Maximilians–Universität Medizinische Fakultät, Munchen, Bavaria, Germany, 1923; died in St. Luke's Hospital Jan. 19, aged 62, of adenocarcinoma of the sigmoid colon.

Lang, Maurice Daniel Ⓜ Bellflower, Calif.; Louisiana State University School of Medicine, New Orleans, 1936; interned at the Charity Hospital in New Orleans; member of the American Academy of General Practice; founder of the Lakewood General and Bellwood General hospitals, of which he was medical director; died Jan. 31, aged 50.

Laue, Richard John Ⓜ Van Nuys, Calif.; University of Southern California School of Medicine, Los Angeles, 1945; interned at the Los Angeles County Hospital; served a residency at the Veterans Administration Center in Los Angeles; an officer in the medical corps of the U. S. Naval Reserve during the Korean War; on the staff of the Valley Hospital; died Jan. 13, aged 39, of coronary thrombosis.

Lawrence, William Henry, Savannah, Ga.; Columbia University College of Physicians and Surgeons, New York City, 1899; specialist certified by the American Board of Surgery; fellow of the American College of Surgeons; served overseas during World War I; for many years associated with the Overlook Hospital in Summit, N. J., of which he was founder; died in the Memorial Hospital Jan. 10, aged 81.

Leary, John Berchmans Ⓜ Arlington, Va.; Temple University School of Medicine, Philadelphia, 1939; interned at the Misericordia Hospital in Philadelphia; served a residency at St. Joseph's Hospital in Baltimore; formerly a fellow in internal medicine at the Lahey Clinic in Boston; past-president of the Arlington County Medical Society; member of the American Psychiatric Association; veteran of World War II; associated with the Arlington Hospital, where he died Jan. 1, aged 47, of coronary occlusion.

Lemon, Frederick Franklin Ⓜ Salina, Kan.; Beaumont Hospital Medical College, St. Louis, 1901; died in the Asbury Hospital Jan. 19, aged 84.

Lewis, Thomas Theodore, Bluefield, W. Va.; Meharry Medical College, Nashville, Tenn., 1931; interned at George W. Hubbard Hospital of Meharry Medical College in Nashville, Tenn.; died Jan. 30, aged 55.

Liebson, Michael, Passaic, N. J.; Baltimore Medical College, 1908; for many years associated with the Beth Israel Hospital, where he died Jan. 27, aged 76, of acute myocardial infarction.

Lindberg, Arvid Claus Ⓜ Minneapolis; University of Minnesota College of Medicine and Surgery, Minneapolis, 1908; died Jan. 20, aged 81.

Luckey, Harold Adair, Columbia City, Ind.; Indiana University School of Medicine, Indianapolis, 1932; affiliated with Luckey Hospital in Wolf Lake; died in the Whitley County Memorial Hospital Jan. 19, aged 63.

Du Bois, Charles Frederick, Alma, Mich.; Rush Medical College, Chicago, 1916; fellow of the American College of Surgeons; died Jan. 28, aged 70, of generalized peritonitis.

Dutton, Loraine Orr, El Paso, Texas; University of Tennessee College of Medicine, Memphis, 1931; member of the American Academy of Allergy and the American College of Allergists; director of the clinical laboratory of Providence Memorial Hospital; died Jan. 23, aged 61.

Edmundson, Harry Clay Ⓜ Fairfield, Ala.; Birmingham Medical College, 1915; formerly associated with the U. S. Public Health Service; veteran of World War I; associated with the Lloyd Noland Hospital; died Jan. 21, aged 66.

Edwards, Trinidad M. Ramos Ⓜ New Orleans; Tulane University School of Medicine, New Orleans, 1942; interned at the Methodist Hospital in Dallas, Texas; served a residency at the Shriners Hospital for Crippled Children in Chicago and the Charity Hospital of Louisiana in New Orleans; specialist certified by the American Board of Orthopedic Surgery; veteran of World War II; associated with the Charity, Sara Mayo, and the Crippled Children's hospitals, and the Southern Baptist Hospital, where he died Jan. 18, aged 40.

Falkenstein, Alfons Philipp Ⓜ Salem, Ohio; Rheinische Friedrich-Wilhelms-Universität Medizinische Fakultät, Bonn, Prussia, Germany, 1938; specialist certified by the American Board of Pathology; member of the College of American Pathologists, American Association of Pathologists and Bacteriologists, and the American Society of Clinical Pathologists; deputy coroner of Columbiana County; served on the staffs of the Alliance City (Ohio) Hospital, Central Clinic and Hospital, and the Salem City Hospital; died Jan. 19, aged 51, of injuries received in an automobile accident.

Feinberg, Albert Robins Ⓜ Wilkes-Barre, Pa.; Jefferson Medical College of Philadelphia, 1924; veteran of World War II; past-president of the Luzerne County Medical Society; a member of the city board of education; on the staff of the Mercy Hospital; died in the Graduate Hospital of the University of Pennsylvania in Philadelphia, Jan. 26, aged 58.

Fox, Earl William Ⓜ Hailey, Idaho; Barnes Medical College, St. Louis, 1908; member of the American Academy of General Practice; died Jan. 25, aged 72.

Fremstad, Joseph, Denham Springs, La.; St. Louis College of Physicians and Surgeons, 1906; veteran of World War I and the Spanish-American War; died in the Baton Rouge General Hospital Jan. 23, aged 87.

Ganzhorn, Edwin Carl Ⓜ Ann Arbor, Mich.; University of Michigan Homeopathic Medical School, Ann Arbor, 1915; member of the American Academy of General Practice; veteran of World War I; county physician; associated with Beyer Memorial Hospital, Ypsilanti, and St. Joseph's Mercy Hospital; died Jan. 17, aged 68, of acute coronary thrombosis.

Garrison, William Miles Ⓜ Silver Spring, Md.; College of Physicians and Surgeons, Baltimore, 1902; member of the American Trudeau Society; served on the faculty of his alma mater; formerly superintendent of the Belmont Sanatorium in St. Clairsville, Ohio; died in Baltimore in February, aged 81.

Gregory, Arthur Britton, Monroe, La.; University of Tennessee College of Medicine, Memphis, 1914; died Jan. 27, aged 73.

Grier, Charles Talmadge Ⓜ Carthage, N. C.; North Carolina Medical College, Charlotte, 1910; served in France during World War I; died Jan. 18, aged 71.

Haas, Toxey Daniel Ⓜ Mobile, Ala.; University of Alabama School of Medicine, 1912; veteran of World War I; for many years county physician; died Jan. 22, aged 72.

Haller, William James, Lindale, Ga.; New York Homeopathic Medical College and Flower Hospital, New York City, 1924; died in Cedartown Jan. 11, aged 61.

Hammond, George Willis, Newnan, Ga.; Atlanta School of Medicine, 1913; past secretary-treasurer of the Coweta County Medical Society; died Jan. 11, aged 73.

Harris, Robert Dozier, Lawrenceville, Ga.; University of Georgia Medical Department, Augusta, 1932; interned at the University Hospital in Augusta; past-president of St. Johns County (Fla.) Medical Society; died Jan. 21, aged 51.

Holman, Marguerite, Jamestown, N. Y.; Boston University School of Medicine, 1920; for many years physician in the public school system in Jamestown; died in the Jamestown General Hospital Jan. 20, aged 68, of cancer.

Holzman, Earl Ernest Ⓜ Pacific Palisades, Calif.; University of Wisconsin Medical School, Madison, 1948; interned at Los Angeles County Hospital, where he served a residency; specialist certified by the American Board of Pediatrics; formerly an officer in the medical corps of the U. S. Air Force Reserve; was electrocuted Jan. 28, aged 35, when he cut into an electric conduit with a buzz saw.

Hornby, Debora Clute, Schenectady, N. Y.; Woman's Medical College of the New York Infirmary for Women and Children, New York City, 1890; died Jan. 18, aged 91.

City, where he served a residency; served a residency at the Beth Israel Hospital; specialist certified by the American Board of Urology; certified by the National Board of Medical Examiners; member of the American Urological Association; fellow of the American College of Surgeons; veteran of World War II; served on the faculty of his alma mater; associated with Mount Sinai Hospital; died Jan. 22, aged 45.

Robbins, Benjamin Howard Ⓜ Nashville, Tenn.; Vanderbilt University School of Medicine, Nashville, 1933; specialist certified by the American Board of Anesthesiology; member of the American Society of Anesthesiologists; president of the Southern Society of Anesthesiology; professor of anesthesiology and associate professor of pharmacology, Vanderbilt University School of Medicine: affiliated with St. Thomas Hospital and the Vanderbilt University Hospital, where he died Jan. 10, aged 55.

Rock, Timothy Francis Ⓜ Nashua, N. H.; Tufts College Medical School, Boston, 1907; member of the Industrial Medical Association; fellow of the American College of Surgeons; past-president of the New Hampshire Medical Society and the Hillsboro County Medical Society; for many years chairman of the city board of health and city physician; affiliated with Nashua Memorial and St. John's hospital; died in Miami, Fla., Jan. 10, aged 75.

Rounds, Clara Wood, Mesa, Ariz.; Bennett Medical College, Chicago, 1904; died in the Southside District Hospital Jan. 9, aged 82.

Ryon, James Barry Ⓜ Annapolis, Md.; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1921; retired from the U. S. Public Health Service April 1, 1956; died in Baltimore Jan. 15, aged 61.

Savre, Samuel, Osage, Iowa; Drake University College of Medicine, Des Moines, 1908; died Jan. 11, aged 83.

Schlemer, John Henry, Detroit; University of Michigan Medical School, Ann Arbor, 1923; also a lawyer; member of the American Academy of General Practice; past-president of the Wayne County Academy of General Practice; served on the editorial board of the *Detroit Medical News;* associated with the Grace Hospital; died Jan. 14, aged 64, of hypertensive heart disease.

Sprague, John Perley Ⓜ Minocqua, Wis.; Northwestern University Medical School, Chicago, 1903; served on the faculty of his alma mater; for many years professor of hygiene and physical education at Grinnell (Iowa) College; veteran of World War I; formerly on the staff of the Illinois Masonic Hospital in Chicago; founder and owner of Camp Minocqua for Boys; died in Orlando, Fla., Jan. 28, aged 86.

Stone, Gideon Willis Ⓜ Knoxville, Tenn.; Lincoln Memorial University Medical Department, Knoxville, 1917; veteran of World War I; died in the Presbyterian Hospital Jan. 24, aged 72.

Sullenberger, Samuel De Vault Ⓜ Dandridge, Tenn.; University of Tennessee College of Medicine, Memphis, 1940; interned at the Methodist Hospital in Memphis; member of the American Academy of General Practice; past-president of the Flying Physicians Association; veteran of World War II and was awarded the Bronze Star; owner of the Sullenberger Clinic and Hospital; died in St. Mary's Hospital, Knoxville, Jan. 16, aged 46.

Thompson, Edward Henry, Levittown, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1910; associated with the Hahnemann and St. Mary's hospitals in Philadelphia; died Jan. 17, aged 74, of chronic myocarditis.

Tuffley, Frank Sylvester, Boscobel, Wis.; Rush Medical College, Chicago, 1903; died Nov. 12, aged 83, of myocardial infarct.

Vaudreuil, William Francis Ⓜ Rice Lake, Wis.; University of Wisconsin Medical School, Madison, 1940; interned at St. Luke's Hospital and served a residency at the Miller Memorial Hospital in Duluth, Minn.; past-president of the Barron–Burnett–Sawyer–Washburn Counties Medical Society; member of the American Academy of Medicine; veteran of World War II; associated with the Lakeside Methodist and St. Joseph's hospitals; died Jan. 13, aged 45.

Verner, William Wiswell, Madeira Beach, Fla.; Hahnemann Medical College and Hospital of Philadelphia, 1901; Medico-Chirurgical College of Philadelphia, 1903; for many years practiced in New York City and was associated with the Veterans Administration; died in Dunedin Jan. 11, aged 84.

Vershbow, Nathan Ⓜ West Hartford, Conn.; Tufts College Medical School, Boston, 1919; veteran of World War I; on the courtesy staff of the Hartford (Conn.) Hospital; died Jan. 8, aged 72, of coronary heart disease.

Walker, William Archibald Ⓜ Tulsa, Okla.; University of Oklahoma School of Medicine, Oklahoma City, 1927; member of the American Academy of General Practice; interned at the Henry Ford Hospital in Detroit; formerly physician for the public schools in Tulsa; assistant plant physician for Douglas Aircraft Company; died Dec. 31, aged 67.

Luse, Ralph Frank Ⓜ Clinton, Iowa; State University of Iowa College of Medicine, Iowa City, 1912; served as president of the Clinton County Medical Society; veteran of World War I; died in the Mercy Hospital Fort Dodge, Jan. 17, aged 74.

Long, Randolph Nelson Ⓜ Selma, Ala.; Tulane University School of Medicine, New Orleans, 1935; specialist certified by the American Board of Radiology; member of the Radiological Society of North America and the American College of Radiology; veteran of World War II; interned at St. Elizabeth's Hospital in Richmond, Va.; on the staffs of Good Samaritan, Selma Baptist, and Vaughan Memorial hospitals; died Jan. 30, aged 49.

McCharen, Littleton Lane Ⓜ West Point, Miss.; Tulane University School of Medicine, New Orleans, 1941; interned at the Southern Baptist Hospital in New Orleans; veteran of World War II; died Feb. 7, aged 46.

McClure, Earl Watson, St. Petersburg, Fla.; Western Reserve University School of Medicine, Cleveland, 1920; died Jan. 18, aged 72.

McKee, Walter Caraway Ⓜ Chicago; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1910; specialist certified by the American Board of Pediatrics; member of the American Academy of Pediatrics; past-president of the alumni association of his alma ater; affiliated with the Children's Memorial, ugustana, Ravenswood, and Henrotin hospitals; died in Cleveland Heights, Ohio, Feb. 3, aged 73.

McNealy, Frances Evelyn McLean; Tujuna, Calif.; College of Physicians and Surgeons, Los Angeles, 1918; died in January, aged 66.

Maginot, Robert Wendell Ⓜ Houston, Texas; Baylor University College of Medicine, Houston, 1949; interned at the University of Texas Medical Branch Hospitals in Galveston; member of the American Academy of General Practice; an officer in the medical corps of the U. S. Army Reserve from October, 1952, to October, 1954, died Jan. 16, aged 37.

Mai, Frederick Maximilian, Jamaica, N. Y.; Julius-Maximilians Universität Medizinische Fakultät, Wurzburg, Bavaria, Germany, 1920; interned at the Rockaway Beach (N. Y.) Hospital; died Dec. 28, aged 67, of cerebral hemorrhage.

Markland, James David Ⓜ Tulsa, Okla.; University of Tennessee College of Medicine, Memphis, 1936; interned at the Bethany Methodist Hospital in Kansas City, Kan.; veteran of World War I; served as a director for Hillcrest Medical Center; died Jan. 25, aged 65.

Martin, Lee Roy Ⓜ Council Bluffs, Iowa; Creighton University School of Medicine, Omaha, 1936; interned at the Mercy Hospital in Council Bluffs; member of the Industrial Medical Association; past-president of the Pottawattomie County Medical Society; past-vice-president of the American Association of Railway Surgeons; associated with Mercy Hospital; died Jan. 24, aged 48, of leukemia.

Mautz, George John Ⓜ Springfield, Ill.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1907; past-president of the Sangamon County Medical Society; member of the staffs of St. John's Hospital and Memorial Hospital, where he died Jan. 23, aged 79, of dissecting aortic aneurysm.

Middleton, William E., Starke, Fla.; University of the South Medical Department, Sewanee, Tenn., 1900; died in the Bradford County Hospital Dec. 22, aged 82, of cerebrovascular accident.

Miller, Rea Provost Ⓜ Pittsburgh; University of Louisville (Ky.) School of Medicine, 1940; interned at the Passavant Hospital; died Jan. 7, aged 52, of coronary occlusion.

Miller, Robert Pumphry, Jamaica, N. Y.; Kansas City (Mo.) Homeopathic Medical College, 1896; died in Jamaica Jan. 23, aged 91, of coronary occlusion.

Millus, Felix Lawrence Jr., Brooklyn; New York University College of Medicine, New York City, 1953; interned at the Methodist Hospital in Brooklyn, where he served a residency; veteran of World War II; certified by the National Board of Medical Examiners; on the staffs of the Methodist Hospital and the Samaritan Hospital; died Feb. 7, aged 35, of a heart attack.

Mitchell, Fred L., Orient, S. D.; Homeopathic Medical College of Missouri, St. Louis, 1899; died Jan. 8, aged 86.

Mitchell, Louis Albert Ⓜ Newark, Ohio; University of Minnesota Medical School, Minneapolis, 1915; veteran of World War I; specialist certified by the American Board of Internal Medicine; member of the American Trudeau Society and the American Society of Clinical Pathologists; fellow of the American College of Physicians; past-president of the Licking County Tuberculosis and Health Association; served on the staff of the Newark City Hospital; member of the board of trustees of Licking County Tuberculosis Sanatorium; member of the board of directors of the First National Bank of Newark; died Jan. 17, aged 71.

Narins, Lester Milton Ⓜ New York City; Long Island College of Medicine, Brooklyn, 1939; interned at the Mount Sinai Hospital in New York

FOREIGN LETTERS

AUSTRIA

Chronic Insomnia.—At the meeting of the Society of Physicians in Vienna on Dec. 4, V. E. Frankl stated that while patients with sleeping disturbances are routinely treated with sedatives, hypnotics, and tranquilizers which are intended to induce sound sleep but which often deprive the patients of their freshness and alertness the next day it is also possible to treat such patients with stimulants, analeptics, and energizers which will increase wakefulness during the day and indirectly increase their sleepiness and the soundness of their nocturnal sleep. Instead of taking sleeping drugs at night the patients take methylphenidate in the morning and at noon. This procedure, which the speaker described as paradoxical medication, proved successful in the outpatient department even in patients with chronic and severe insomnia in whom soporifics failed. Its advantage lies in the fact that this therapy aids the indicated psychotherapy inasmuch as the patient regains his confidence in being able to guide his sleeping rhythm again and is released from his anxiety about the consequences of a sleepless night.

Forced Alimentation with Antibiotics.—At the same meeting Drs. R. Boller and H. Partilla stated that experiences in veterinary medicine showed that an increase in weight and acceleration in growth can be achieved in young animals if antibiotics are given in addition to the regular diet. They therefore added tetracyclines (about 1/30 of the daily therapeutic dose) to the regular diet given to various patients. A good increase of weight was achieved, but in those patients who were given a forced alimentation diet with or without antibiotics no significant increase of weight occurred.

Patients with subacidity and anacidity reacted particularly well to antibiotics, and therefore patients who had undergone gastric resection were the chief recipients of this treatment. In a series of 855 such patients, follow-up examinations after one year showed that those who received the antibiotics felt better and had gained more weight than those who received the usual treatment because maintenance of weight and well-being were related. It has been possible to prove after painstaking trials that the inadequate utilization of protein may be compensated by the additional feeding of antibiotics. This was shown in patients with gastric resection, in whom 45% or more of the alimentary albumin was lost with the feces. After the addition of antibiotics to the diet the amount of albumin lost returned to that observed in normal persons.

Nandrolone for Infantile Muscular Atrophy.—At a meeting of the Society of Physicians in Vienna on Jan. 8, Dr. O. Stur reported on three patients with infantile spinal muscular atrophy who were treated with nandrolone phenpropionate, a derivative of testosterone that has a stronger anabolic and a weaker virilizing effect than testosterone itself. The first patient was 18 months old and on admission was unable to sit up or stand up. After two months of treatment with nandrolone he was able to stand up and to walk when given a hand. The electromyogram no longer showed signs of anterior born cell lesions. In the second patient, who had paralyzed arms and legs, the arms and the back muscles improved after six months of nandrolone therapy to such an extent that he could sit up and lift small objects with his arms. In the third patient, who since birth had severe paralysis of the extremities and muscles of the trunk, nandrolone was ineffective. The child died at the age of 10 months. Although the small number of cases does not permit evaluation of the value of nandrolone therapy in infantile spinal muscular atrophy, the results obtained suggest the value of trial on a larger scale.

Haptoglobin Determination and Paternity Suits.—At the same meeting L. Breitenecker pointed out the significance of the haptoglobin types in forensic medicine and emphasized that their determination can be also of clinical importance. This method was used in 21 paternity suits, and one accused man was thereby exonerated. The speaker stated that paternity could be determined by this method in healthy persons with 99 to 99.9% certainty.

The speaker's method was based on high-voltage-zone electrophoresis in starch gel with a running time of five to eight hours and a consecutive peroxydase reaction. It should be possible to reduce the duration to less than half this time with new improved equipment. The haptoglobins are not coupled with other known blood groups and blood factors and are hereditarily transmitted. Since a pure-hereditary parent can transmit only one gene of this characteristic, the characteristics of the child are a combination of those of both parents. In the speaker's case the mother had the 2-2, the accused had the 2-2, but the child had the 2-1 pattern. It must therefore have inherited gene 2 from its

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The items in these letters are contributed by regular correspondents in the various foreign countries.

Weiss, Selma Ⓜ East Orange, N. J.; New York Homeopathic Medical College and Flower Hospital, New York City, 1919; formerly practiced in Newark, where she was associated with the Newark City Hospital; for many years on the staff of the East Orange General Hospital, where she died Jan. 17, aged 65.

Welker, Maurice Eugene, Cincinnati; Eclectic Medical College, Cincinnati, 1912; died in the Bethesda Hospital Jan. 9, aged 73.

Wells, Arthur Marvin Jr. Ⓜ San Antonio, Texas; Vanderbilt University School of Medicine, Nashville, Tenn., 1947; interned at the University of California Hospital in San Francisco; served a residency at the Baylor University Hospital in Dallas, Texas; an officer in the medical corps of the U. S. Naval Reserve from April 1, 1952, to March 28, 1954; died Jan. 9, aged 37.

Wells, Edmond Daniel, Washington, D. C.; University of Louisville (Ky.) Medical Department, 1910; veteran of World War I; served on the staff of the Chesapeake and Ohio Railroad Hospital in Huntington, W. Va.; died Jan. 26, aged 70.

White, John Edmund, Malone, N. Y.; Albany (N. Y.) Medical College, 1910; veteran of World Wars I and II; for many years on the staff of the Alice Hyde Memorial Hospital; died Jan. 1, aged 71, of coronary occlusion.

White, Oliver Thomas, Atlanta, Ga.; Atlanta College of Physicians and Surgeons, 1902; died Dec. 28, aged 81, of probable myocardial infarction and arteriosclerotic heart disease.

Wiechelman, Clement John, Cincinnati; University of Cincinnati College of Medicine, 1911; died Dec. 29, aged 71.

Williams, Dudley Abeel, Providence, R. I.; Boston University School of Medicine, 1900; served on the staff of the Roger Williams General Hospital; died in the Institute of Living, Hartford, Conn., Jan. 16, aged 85.

Williams, Thomas P., Danville, Ill.; Louisville (Ky.) Medical College, 1901; died in the Lakeview Hospital Jan. 20, aged 86.

Williamson, William Harper, Oklahoma City, Okla.; Homeopathic Medical College of Missouri, St. Louis, 1902; for many years associated with the Capitol Hill General Hospital, of which he was founder; died Jan. 6, aged 87.

Willis, Benedict Patrick, Rutherford, N. J.; University and Bellevue Hospital Medical College, New York City, 1912; fellow of the American College of Surgeons; surgical director emeritus at St. Mary's Hospital in Passaic; director of the National Community Bank of Rutherford; died Jan. 30, aged 71.

Wilson, Clyde, Emporia, Kan.; University of Louisville (Ky.) Medical Department, 1910; died in St. Mary's Hospital Jan. 18, aged 75.

Wilson, Russell Fletcher Ⓜ Beloit, Wis.; Southern College of Medicine and Surgery, Atlanta, 1914; specialist certified by the American Board of Radiology; member of the Radiological Society of North America, Inc., and the American College of Radiology; past-president of the Rock County Medical Society; veteran of World War I; served on the staffs of the Swedish-American Hospital in Rockford, Ill., and the Beloit Municipal Hospital, where he was past-president of the staff; died in the Tampa (Fla.) General Hospital Jan. 17, aged 69.

Wolfe, Michael M. Ⓜ Philadelphia; Temple University School of Medicine, Philadelphia, 1917; veteran of World War I; on the staff of St. Joseph's Hospital, where he died Jan. 24, aged 66.

Wolfrom, Carlos Eugene Ⓜ Philadelphia; Jefferson Medical College of Philadelphia, 1926; specialist certified by the American Board of Obstetrics and Gynecology; served on the faculty of his alma mater and the University of Pennsylvania Graduate School of Medicine; fellow of the American College of Surgeons; on the staffs of the Delaware County Hospital in Drexel Hill, Pa., and the Pennsylvania and Lankenau hospitals; died in Jefferson Medical College Hospital Jan. 20, aged 59.

Woltereck, Gustav Herman Ⓜ Baltimore; Johns Hopkins University School of Medicine, Baltimore, 1909; specialist certified by the American Board of Pediatrics; on the staff of the Union Memorial Hospital; died Jan. 22, aged 76, of bronchopneumonia.

Wren, Raphael John Ⓜ Ossining, N. Y.; University and Bellevue Hospital Medical College, New York City, 1906; died Jan. 25, aged 79.

Wunschel, Richard Charles Ⓜ Moline, Ill.; State University of Iowa College of Medicine, Iowa City, 1946; interned at the Moline Public Hospital in Moline, Ill., and served a residency at the Michael Reese Hospital in Chicago; member of the American Society of Anesthesiologists; from September, 1947, to August, 1949, served in the medical reserve corps of the U. S. Army; died Jan. 29, aged 39.

Zimmerman, Clark Benjamin Ⓜ Lewisburg, Pa.; McGill University Faculty of Medicine, Montreal, Que., Canada, 1932; member of the school board; interned at Pottsville (Pa.) Hospital; died in the Community Hospital Jan. 11, aged 54.

this disease has become relatively rare, thanks largely to the heavy taxation of alcohol. Soon after the introduction of barbital in 1903, patients with delirium tremens were given this drug with such satisfactory results that it continues to be given systematically at the Risskov Psychiatric Hospital, where two generations of psychiatrists have remained loyal to it. It is, however, ignored in several countries, and various comprehensive studies of delirium tremens have not included any mention of it. At the Risskov Hospital 0.75 to 1.00 Gm. of barbital is given up to three times at hourly intervals. During the next few days 0.25 to 0.50 Gm. is given two or three times. It is most important that the drug be given as early as possible, without waiting for the development of the classic picture of the disease.

INDIA

Chlorothiazide as a Diuretic.—Lele and Sainani gave chlorothiazide as a diuretic to 32 patients with edema (*J. A. Physicians of India,* vol. 8, January, 1960). Of these 13 had cardiac, 9 renal, 7 hepatic, and 3 nutritional edema. All had general anasarca, and most of them had failed to respond to mercurial diuretics. These patients were told to rest in bed and were given a salt-free diet without restriction of fluids. Body weight was recorded daily, and the 24-hour urine output was measured. When the weight and urine output had been stable for three consecutive days two 500-mg. tablets of chlorothiazide were given twice a day for three consecutive days. A maintenance dosage of one-half tablet twice a day daily or on alternate days was given for 7 to 10 days if there was evidence of reaccumulation of fluid. None of the patients showed any toxic effects during this short-term therapy.

The response was good in 12 of the 13 patients with cardiac edema and fair in the remaining patient. Four patients who had previously proved resistant to mersalyl responded well to chlorothiazide. Of the nine patients with renal edema, three showed a good, one a fair, and five a poor response. The three patients who responded well had normal blood pressure, a blood urea level below 60 mg. per 100 ml., and an absence of red blood cells or casts in the urine. In the patient with a fair response the blood pressure and blood urea levels were higher and urine analysis showed a few red blood cells and granular casts. Those with a poor response had high blood pressure, a blood urea level between 100 and 200 mg. per 100 ml., and red blood cells and granular casts in the urine.

Chlorothiazide was found helpful only in those patients with renal edema in whom the blood pressure and blood urea levels were not greatly elevated and the urine did not show erythrocytes and granular casts. Of the seven patients with cirrhosis of the liver three showed a good, one a fair, and three a poor response. None of the patients developed hepatic precoma or coma as a result of therapy. The three patients with nutritional edema had failed to respond to previous therapy with rest in bed and a high protein diet for 15 days. Their response to chlorothiazide was good. Thus the drug proved effective in patients with cardiac edema, uncomplicated renal edema, hepatic edema, and nutritional edema.

Jaundice and Tuberculosis.—Tandon and Khana studied the effect of jaundice on the course of pulmonary tuberculosis in 30 patients (*J. A. Physicians of India,* vol. 8, January, 1960). The jaundice in all was hepatocellular in nature. The specific antituberculosis treatment was stopped during the period in which the patient had jaundice, which itself was treated in the usual way. The nature of the constitutional disturbance in these patients was the same as in any other patients with hepatocellular jaundice, but the intensity was much less than in a patient with only jaundice. The resting pulse rate decreased but tended to increase after improvement in the jaundice.

Of these patients 25 showed the usual pattern of increase in temperature during the prodromal period. The sedimentation rate returned to normal in 18 of the patients. This effect was, however, transient, and the rate increased to its previous level after the patient recovered from the jaundice. The roentgenographic findings showed no change during the period in which the patient had jaundice. The jaundice could have been due to drug toxicity after the use of para-aminosalicylic acid (PAS) or to the virus of homologous serum jaundice. Drug toxicity was excluded as those patients who were receiving PAS before the onset of jaundice did not develop jaundice again after its restitution. The possibility of homologous serum jaundice could not be excluded. Most of the patients experienced a general feeling of well being and a decrease in the resting pulse rate and average temperature during the period of jaundice. This effect was seen only as long as the jaundice lasted.

SWEDEN

Septic Arthritis from Cortisone.—At the Rheumatological University Clinic in Lund over 2,000 intraarticular injections of cortisone are given yearly, but so far they have given rise to only two cases of Staphylococcus aureus infection of the injected joint. Commenting on these cases Gedda and Juhlin (*Svenska läkartidningen,* Nov. 27, 1959) noted that both patients had malignant rheumatoid arthritis of the knees and that cortisone had previously been given by mouth for some time to both. Such medication might have reduced the patients' natural re-mother and gene 1 from its father. Since the accused did not show this gene he could not have been the father.

BRAZIL

Insecticides Poisoning.—Men working in plants where phosphorus insecticides are manufactured are subject to acute and chronic poisoning. Certain precautions are necessary to prevent this. Dr. Francisco Perrone (*An. paulist. med. e cir.*, December, 1959) stated that poisoning by phosphorus insecticides may occur by absorption through the skin, by breathing contaminated vapor or dust, and by ingestion. Prospective workers must be alerted to the dangers without causing undue alarm. Any kind of work is dangerous when performed without regard to appropriate precautions.

Before starting to work in the morning the worker puts on work clothes furnished by the company and consisting of cotton shirt, shorts, overalls, long stockings, half boots, rubber gloves, head protector, spectacles, and mask. Before lunch the worker takes a shower and puts on his street clothes. Back at work he again changes, and before leaving the plant he takes another shower and puts on his own clothes. Every morning he receives a clean set of working clothes. As an early indication of poisoning the patient may have slight or violent headache quickly followed by mental clouding. He partially or completely loses consciousness. There is profuse sweating. Breathing becomes rapid but shallow, tachypnea sets in, and the pulse rate increases to 140 or more beats per minute. The blood pressure, at first normal or nearly so, is quickly increased. Ocular accommodation and light reflexes frequently disappear or decrease with occurrence of myosis. Tendinous reflexes are exaggerated. Cholinesterase activity decreases. If therapeutic measures are not immediate, energetic, and adequate, pulmonary edema sets in.

The recommended treatment includes (1) intramuscular injection of atropine; (2) venesection if the blood pressure is high; (3) intravenous injection of 0.25 mg. of ouabain; (4) cardiopulmonary analeptics such as lobeline, cardiazol, or coramine as needed; (5) immediate transportation to a hospital of patient, who must be kept as quiet as possible; (6) superficial bath with weak solution of sodium bicarbonate if patient is toxic; (7) inhalation of oxygen; (8) intravenous injection of hypertonic dextrose solution; (9) copious intestinal enema with magnesium sulfate if patient is unable to swallow; (10) magnesium sulfate by mouth if patient can swallow; (11) intramuscular injection of phenobarbital if there is psychomotor agitation; and (12) blood transfusion in some patients. Milk should not be taken during working hours because the milk fats favor absorption of phosphorated compounds. Alcohol should also be avoided.

DENMARK

Dilatation of the Prostate.—Dr. B. Viking (*Nord. med.*, Dec. 17, 1959) reported a series of 93 patients who underwent dilatation of the prostate. He found this procedure suitable for small or moderately large adenomas of the prostate, although large adenomas required a more radical operation. Although many of the 93 patients were debilitated or handicapped by heart disease or other ailments, this treatment was on the whole well tolerated. It should, however, be deferred so as to give time for improvement of bladder evacuation or a faultily compensated heart. Mental disease, notably a psychosis, is a contraindication. Although the technique is simple, a certain manipulative dexterity is necessary, and so is the experience which enables the operator to meet complications by appropriate countermeasures. The sequel to this treatment was death in four patients, late hemorrhage in eight, epididymitis in six, and incontinence of urine in three.

Peroral Treatment of Diabetes.—Since April, 1956, department C of the Odense Hospital has given 153 diabetics various drugs by mouth, notably carbutamide and tolbutamide. Commenting on these drugs, Dr. Karen Astrom (*Ugesk. laeger*, Jan. 7, 1960) noted that most observers have found tolbutamide to be better tolerated than carbutamide, whose antidiabetic effect is greater however. Cutaneous reactions in 12 patients necessitated the abandonment of this treatment in 5 of them.

Leukocyte and differential counts were made on 133 patients, in several of whom a slight initial fall of the leukocyte count was followed by a return to the normal level. Thrombocyte counts in 71 patients showed a slight decrease during treatment, and one patient treated with tolbutamide developed serious thrombopenia associated with hemorrhages, fever, and involvement of the joints, but he recovered. The erythrocytes showed no changes for which the treatment could be held responsible. There were dyspeptic symptoms in 10 of the carbutamide-treated and in 1 of the tolbutamide-treated patients. A search for proteinuria failed to show a relationship between its onset and this treatment, but there were three patients in whom the institution of carbutamide treatment provoked hypoglycemia, as indicated by shivering, sweating, and a sense of lassitude not amounting to collapse. Because of the risk of complications, the peroral long-term treatment of diabetes requires close and constant supervision.

Treatment of Delirium Tremens with Barbital.—In the last two years delirium tremens has increased in frequency in Denmark, according to Dr. B. F. Sörensen (*Danish M. Bull.*, vol. 6, November, 1959), who qualifies this statement with the opinion that

CORRESPONDENCE

POLIOMYELITIS VACCINE

To the Editor:—Dr. Langmuir's paper, "Progress in Conquest of Paralytic Poliomyelitis," in The Journal, Sept. 19, 1959, ends on a note of optimism: "We can look forward with confidence to the complete elimination of the paralytic forms of the disease." This expectation is not justified by the current estimates of the antiparalytic value of the Salk vaccine recorded in Francis' report and in various subsequent studies, including those of Dr. Langmuir himself, in most of which failures were reported in 20 to 30% of patients vaccinated. Experience in 1959 indicated an alarming increase of paralytic poliomyelitis in the United States. As of Oct. 9, 4,013 patients with this form of the disease have been officially reported, while there were only 1,931 reported for the same period in 1958 (Morbidity and Mortality, vol. 8, no. 39, Public Health Service, 1959).

The defects of the Salk vaccine are brought out by the reports of the Poliomyelitis Surveillance Section of the Communicable Disease Center of the Public Health Service. In the Oct. 16, 1959, issue of the reports 595 cases of paralytic poliomyelitis were recorded in persons who had received three or more doses of vaccine. Applied to the 3,389 paralyzed patients of whom the vaccination record was known, the data show that 17.5% had had the full immunizing course. Another 302 patients had had two inoculations. Comparison of the 1958 and 1959 statistics indicates that there may be over 6,000 cases of paralytic poliomyelitis by the end of the calendar year; more than 1,000 of these will probably have occurred in thrice vaccinated persons.

While I have no thought of suggesting abandonment of the Salk vaccine, I do wish to urge the official sanction by the Public Health Service of live attenuated vaccine at the earliest possible moment. The Oct. 17 issue of The Journal contains Dr. Sabin's review of this type of immunization, which has been used on an enormous scale in other parts of the world with excellent results and with safety to the immunized subjects and to the community. Since there is no interference between the dead and live vaccines there appears to be no valid reasons why both should not be used in the same persons. Added protection to an important degree against paralysis should certainly follow.

Harold K. Faber, M.D.
2351 Clay St.
San Francisco.

This item was referred to the author of the original article, and the following reply was received.

To the Editor:—By quoting only part of the last paragraph of the paper, Dr. Faber has missed the main issue. The paper as a whole emphasizes the seriousness of the situation and calls for leadership and action. The "note of optimism" was clearly contingent on the effective exercise of this leadership. At the time of presentation, June, 1959, the serious implications of the 1958 epidemics in Detroit, northern New Jersey, and the Virginia mountains were painfully apparent. A prediction for 1959 was studiously avoided. The number and severity of the outbreaks during the past summer further emphasize the problem and the need for action. The character of this action should be determined by a careful evaluation of the epidemiological evidence. It was and remains my view that with the attainment of an effective degree of immunity in the whole population, paralytic poliomyelitis will be eliminated. The full potential of Salk vaccine to achieve this goal has not yet been adequately tested.

Dr. Faber implies that our present difficulties stem in large part from the inadequacy of the Salk vaccine. He asserts there would be a high proportion of vaccine failures "even with universal application of the Salk vaccine." He urges resorting to live poliovirus vaccines with use of both the dead and live vaccines in the same persons. The epidemiologic evidence does not support his pessimism.

The main thesis of my paper was the concentration of cases of paralytic poliomyelitis in 1958 among unvaccinated preschool children and the localization of epidemics and outbreaks with high attack rates to sharply defined groups of lower economic status having the lowest levels of immunization. This epidemiologic pattern was again clearly apparent in 1959 and is strikingly different from that observed in the prevaccine period. Then poliomyelitis was essentially ubiquitous and certainly was no respector of upper socioeconomic groups. The implications of these facts are clear. The immunity of those groups that are now at greatest risk must be raised to levels as high or perhaps higher than the levels in the rest of the population. Until this is achieved it is not possible to conclude, as Dr. Faber seems to have done, that our present problems are due to inadequate or only partially effective vaccine.

With regard to estimates of vaccine effectiveness, published statements from the Communicable Disease Center have been purposefully conservative. In the present paper an effectiveness of only 75%

sistance to infections. The septic arthritis induced by the injections was treated by aspiration but not by any antibiotic deposited in the inflamed joint. Antibiotics were, however, given by mouth, and signemycin given in this way was effective and did not cause troublesome side-effects. The strict adherence to asepsis always necessary for intra-articular injections should be observed more than ever when the patient has already been given cortisone by mouth, and in such patients it may be well to make use of prophylactic chemotherapy.

Truxal for Alcoholic Psychoses.—Alsén and Frey (*Svenska läkartidningen*, Nov. 27, 1959) gave Truxal to a series of 40 patients suffering from severe alcohol poisoning which in 27 was manifested by delirium tremens and in 13 by the predelirium state with auditory hallucinations. When 20 mg. had been given intramuscularly and had made the patient quiet and drowsy he could be given 30 to 50 mg. of the drug three times daily by mouth, but if hallucinations persisted the injections may have had to be continued, 20 mg. being given three or four times daily. In only one patient did the total quantity of the drug given exceed 1 Gm. The potency of Truxal was not gauged by strictly followed double-blind tests, but a comparison of the present material with earlier material observed in the same hospital gave the impression that Truxal marks an important advance in the treatment of alcohol poisoning. It may prove to be superior to the other tranquilizers such as promethazine, chlorpromazine, meprobamate, and serpasil.

Flumidin for Herpes Zoster.—Dr. B. Schersten (*Svenska läkartidningen*, Dec. 18, 1959) treated patients who had virus infections including herpes labialis, herpes ophthalmicus, and herpes zoster with Flumidin. Intramuscular and oral administration were tried. The latter ultimately replaced the former, and 100 mg. of the drug in tablet form was given three times daily for six days. In view of the drug's low toxicity and rapid elimination, it is safe to double the above dosage and prolong its administration beyond six days if necessary. Tests of the blood, liver, and kidneys during this treatment were reassuring, and the only side-effects recorded were slight discomfort experienced by one patient and quickening of the pulse noted in another in whom 250 mg. had been given intramuscularly. In most patients adequate treatment with this drug was followed by cessation of pain after a couple of days with a return of the temperature to normal.

Heparin for Prevention of Thrombosis.—Because of 11 patients with pulmonary embolism, most of whom died, in the surgical section of the Norrköping Hospital in 1958, the staff decided to make tests with subcutaneous injections of heparin as a postoperative measure for elderly and bedridden patients. Dr. B. Holmqvist and co-workers (*Nord. med.*, Dec. 17, 1959) checked these tests in 15 patients by measuring the rate of coagulation before and after the subcutaneous injection of a water-soluble 25% solution of heparin, the dose of which was 250 to 300 mg. Twenty-four hours after an injection only a few of the patients still showed a slight prolongation of coagulation. At least two days had passed after an operation before the injection was given. In only one patient could the heparin possibly have been harmful and have led to macroscopic hematuria, but such a sequel can quickly be combated by intravenously injected protamine sulfate. With a dose of 250 mg. of heparin every day or every other day, it should not be necessary to measure the rate of coagulation in any given patient as a check on this treatment. The resulting anticoagulant action is more sustained by subcutaneous than by intravenous injection. The only local complications were small hematomas observed in two patients.

UNITED KINGDOM

High Profit on Drugs.—In a report to Parliament the Auditor-General cast doubt on the effectiveness of the pharmaceutical industry's voluntary price regulation scheme. The scheme was intended to secure fair and reasonable prices for proprietary preparations. The Auditor General found that a high rate of profit accrued to a large section of the industry. The profit of one firm apparently exceeded 100% of the capital used. The three-year trial period of the scheme ends in June. The average cost of a prescription in 1957 was 83.5 cents and in 1958 was 91.5 cents. The proportion of proprietary drugs continued to increase and now accounts for over 70% of the cost of ingredients of all prescriptions dispensed under the National Health Service. The Service's estimated cost of such drugs not therapeutically superior to standard preparations increased from 56 million dollars in fiscal year 1955-1956 to 84 million dollars in fiscal year 1958-1959. A handbook on prescribing which gives the comparative costs of standard and proprietary drugs will be distributed soon to physicians.

Doctor Draft.—The call of doctors eligible for national service will continue until the end of 1960. It is planned that compulsory recruitment will come to an end at that time. As no doctors who became or will become provisionally registered after Jan. 1, 1960, and none of those whose deferment extends beyond the end of 1960 are likely to be needed except in an emergency, the pool from which physicians are to be recruited for national service is a contracting one. Fortunately, the pool from which hospitals draw their junior medical staff should gradually expand.

neither proves that the lowered mortality rate from anesthesia at MacDonald House was due to improvement in the skill of the personnel administering anesthetics nor establishes the superiority of physician anesthetists to nurse anesthetists. A careful perusal of the graphs in the article shows that mortality decreased concurrently with the increased use of conduction anesthesia, which could as readily be assumed to be the significant factor.

A word should be spoken in behalf of the nurse anesthetists and in the interest of good anesthesia coverage for hospitals. Dr. Cull's paper by implication impugns the value of the well-trained conscientious nurse anesthetist and, like many even more biased utterances, will tend to discourage the recruiting and training of nurse anesthetists, who are sorely needed to meet the demands of hospitals throughout the country.

It is necessary for many hospitals and surgeons to depend on nurse anesthetists because of the shortage of physician anesthetists, and I doubt whether it would be desirable to have all anesthetics administered by physicians. Such a system would probably not be safer and would certainly be more expensive for the patient.

An ideal situation would be one in which fully-trained nurse anesthetists worked under the direction of a physician anesthetist. In smaller institutions, if the chief of surgery is concerned about maintaining a good, safe anesthesia service and will take an interest in and support his staff of nurse anesthetists, the latter can provide a service comparable to that given by the best physician anesthetists and better than the average.

Anesthesiology is in itself not a science but a technical discipline combining knowledge and principles gleaned from the several basic sciences. I am persuaded that intelligent graduate nurses can master the art of administering anesthetics as well as any physician anesthetist and can acquire a background in basic science extensive enough to allow them to handle all but the most unusual situations. In support of this contention I offer the following data from our own surgical and obstetrical services, which are maintained only by full-time nurse anesthetists under the supervision of the chief of surgery.

From 1950 to 1959 inclusive, 31,949 anesthetics were given in the hospital. In this period one death was attributable to anesthesia, that of a 23-year-old woman who went into irreversible circulatory collapse one hour after administration of spinal anesthesia for a minor gynecological procedure. Autopsy failed to reveal the cause of death. In the same period there were 8,484 deliveries with one maternal death due to lower nephron nephrosis after severe shock in a young woman who had abruptio placentae. This death was unrelated to the anesthesia.

I do not regard the nurse anesthetist as only a stopgap until enough physician anesthetists are available to meet our needs. I am convinced that she has a permanent and essential place on the hospital team. I beg teaching hospitals to restore the abandoned programs and to institute new ones where they do not now exist. Otherwise, a situation will soon prevail in which only a few institutions served by well-trained physician anesthetists will be able to provide excellent anesthesia service while the average quality of anesthesiology throughout the country gradually declines as the number of nurse anesthetists diminishes from lack of a renewed supply.

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TREATMENT OF SUPERFICIAL THROMBOPHLEBITIS WITH PHENYLBUTAZONE

To the Editor:—In The Journal, Jan. 16, 1960, page 229, the author of the article entitled "Treatment of Superficial Thrombophlebitis with Phenylbutazone" presented his results as follows: "I had occasion to treat 25 patients with thrombophlebitis at the U. S. Army Hospital, Fort Sill, Okla., in 1956 and 1957 and about 15 patients in private practice since that time. All patients responded promptly to short courses of phenylbutazone therapy, and no side-effects from the drug were observed in any. Three of the more difficult cases are presented."

He then proceeded to report briefly on three patients, all of whom appear to have had deep thrombophlebitis (all three had edema), in spite of the title of the article.

There are two main points about which I would like to take issue. First, the paragraph quoted above along with the case reports leads one to believe that some 40 patients with deep and superficial thrombophlebitis "responded promptly to short courses of phenylbutazone therapy" without anticoagulant therapy, which is mentioned only in case one. Phenylbutazone is an analgesic and may possibly be an antiphlogistic, but it has never been shown to be an anticoagulant. Anticoagulant therapy must remain the treatment of choice in patients with deep vein thrombosis, if only because of the danger of pulmonary emboli. It has also been shown to hasten recovery and to decrease the incidence of the postphlebitic syndrome. Superficial thrombophlebitis, much less likely to cause pulmonary emboli, often subsides without anticoagulant therapy but may require heparin in some instances.

Second, my own experiences with phenylbutazone administered in doses of 200 mg. three times a day without anticoagulants to patients with or more was claimed. These estimates are based on evaluations of the poliomyelitis surveillance case reports being submitted by all 50 states matched with estimates of immunization levels in the population derived from a random sample of families throughout the country. Such data are not precise and warrant cautious appraisal, but as experience accumulates all the evidence points toward the maintenance of immunity in the vaccinated portion of the population. Estimates of effectiveness can now be revised upward. Final figures for 1958 data point to immunity for three or more doses in the range of 90%. Preliminary data for 1959 indicate an even higher degree of protection for those who have received four doses. The explanation for the seemingly large numbers of triply vaccinated paralyzed patients, about 17% of all paralyzed patients, is simply that a substantial proportion of the young population of the country, about 70%, has received three or more doses of vaccine.

With regard to live poliovirus vaccines, the Public Health Service has already taken a number of positive steps directed toward establishing criteria for licensing of these vaccines for sale in interstate commerce. A special advisory committee appointed by the Surgeon General more than one year ago has made substantial progress in developing detailed protocols and recommendations for manufacturing and testing. Difficult problems are still to be anticipated regarding criteria for safety and standards for consistency of production. Many months may pass before a licensed product becomes available in this country.

In the meantime, an immunizing procedure of known effectiveness is available in adequate supply and deserves to be used far more than it has to date.

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IATROGENIC DISEASE CAUSED BY DETERGENTS

To the Editor:—Drs. Teitel and Florman (*J. A. M. A.* 172:329 [Jan. 23] 1960) are unnecessarily conservative in their discussion of the source of infection of their patient with Pseudomonas aeruginosa endocarditis. In my opinion, the cause of the endocarditis was probably that mentioned in the letter, quoted in the article, from the surgeon who had performed the open heart operation on their patient. His letter clearly implies that contamination of benzalkonium chloride used to sterilize a mechanical pump oxygenator was the source of infection and mentions "several other similar cases" which led to a change in the technique of sterilization.

Contamination of detergents by Pseudomonas is a well known phenomenon and in recent years has been the subject of several articles and of annotations in the *Lancet* (2:305 [Aug. 9] 1958) and the *British Medical Journal* (2:436 [Aug. 16] 1958). Keown and others (*J. A. M. A.* 165:781 [Oct. 19] 1957) reported five deaths from infection by Pseudomonas aeruginosa which was traced to contaminated benzalkonium. Shickman and others (*New England J. Med.* 260:1164 [June 4] 1959) reviewed the literature and reported several cases which occurred after cardiac catheterization. An epidemic of Pseudomonas bacteremia which resulted from this phenomenon was reported by Plotkin and Austrian (*Am. J. M. Sc.* 235:621 [June] 1958), and the mechanism of contamination was explored in this and in several other papers (Lowbury, *Brit. J. Indust. Med.* 8:22 [Jan.] 1951, and Anderson and Keynes, *Brit. M. J.* 2:274 [Aug. 2], 1958).

Teitel and Florman seem reluctant to accept the operation as the source of infection because of the 20-week interval between the operation and the first symptoms of illness, but it is well known that Pseudomonas organisms have low pathogenicity for man and that poor host resistance or other unusual circumstances are generally prerequisites for symptomatic illness. Inasmuch as their patient was in relatively good condition, a long period may have been required for the disease to develop. One also wonders whether antibiotics were given to this patient "prophylactically" after operation. Furthermore, it appears from the findings at the second operation that the endocarditis would not have developed but for the nidus of a silk ligature. Thus there are several possible explanations for the slow onset of illness.

I realize that Teitel and Florman were emphasizing therapy rather than etiology in their article, but I think that no opportunity should be lost to point out that dependence on detergents for sterilization can be dangerous under certain conditions. From personal communications I know that more instances of iatrogenic disease caused by detergents have occurred than have been reported in the literature.

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NURSE ANESTHETISTS

To the Editor:—The article by William A. Cull, M.D., entitled "Twenty-Four-Hour Obstetric Anesthesia Coverage" (*J. A. M. A.* 172:416 [Jan. 30] 1960), impels me to comment. While no one can take exception to Dr. Cull's contention that 24-hour coverage of an obstetric service by skilled anesthetists is highly desirable, the evidence he presents

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Stimulation of the Carotid Sinus in Man: I. The Cerebral Response. II. The Significance of Head Positioning. J. F. Toole. Am. J. Med. 27:952-958 (Dec.) 1959 [New York].

The author reports on 39 patients with syndromes compatible with either the cerebral form of carotid sinus reflex hypersensitivity, described by Weiss, or the more recently recognized syndrome of carotid artery insufficiency. The patients were tested in the department of neurology of the Hospital of the University of Pennsylvania, in Philadelphia, in an attempt to determine the relationship between these 2 syndromes. After baseline electroencephalographic and electrocardiographic recordings had been obtained and after the brachial blood pressure had been stable for about 10 minutes, one internal carotid sinus was compressed posteriorly against the cervical spine for 30 seconds, with the patient lying horizontal on the tilt table. If neither electroencephalographic nor clinical effect was produced. the opposite sinus was compressed. If any abnormality was obtained with compression, gentle massage without compression was applied for 30 seconds. Lastly, the ipsilateral common carotid artery was then compressed for 30 seconds. When a cardioinhibitory or vasodepressor response occurred, pressure was either applied more slowly or atropine sufficient to block this undesired reflex was given in doses of 0.4 to 0.6 mg. intravenously. This sequence was repeated on each side with face frontward, then with the face turned to the right, and finally to the left. If no abnormality was elicited with any of these maneuvers, the entire series of steps was repeated after the patient had been tilted rapidly to a head-up position, 70 degrees from the horizontal position, and after blood pressure and cardiac rate had again stabilized.

Of the 39 patients, 5 had a primary neurological response to carotid sinus compression while they were in a horizontal position with the face frontward. Turning of the head with sinus compression evoked abnormality in 5 additional patients, who had negative response to testing with the face frontward. When the test sequence was repeated in the 70-degree position on those who had no reaction while in the horizontal position, only one other patient reacted with his face turned frontward, but turning of the head added 6 more. Thus, the total number of patients in whom a cerebral response to carotid sinus pressure occurred was 17. Ten of 12 reactors who had only one sensitive sinus were further studied, and all had marked stenosis or occlusion of the opposite internal carotid artery.

These findings showed the previously unrecognized influence of head position on response to carotid compression tests. Vertebral artery compression produced by turning the head is postulated to be the basis for this result. It is evident that compression of the carotid artery, rather than carotid sinus stimulation, is the usual test incitant, that head position is an important factor, and that no true reflex is involved in most cases of carotid sinus reflex hypersensitivity. Many cases really fall in the category of carotid artery insufficiency. A unilaterally "sensitive" sinus was found usually to signify stenosis or occlusion of the opposite internal carotid artery.

Thumping of the Precordium in Ventricular Standstill. D. Scherf and C. Bornemann. Am. J. Cardiol. 5:30-40 (Jan.) 1960 [New York].

The authors report on 11 patients, between the ages of 53 and 81 years, in whom the myocardium had been altered by disease leading to varying degrees of hypoxia and in whom ventricular standstill occurred at the New York Medical College Hospital in New York. Electrocardiograms were obtained from these patients during ventricular standstill and when blows to the precordium elicited automatic ectopic beats. The clinical electrocardiographic tracings were compared with experimental tracings obtained from dogs. The observations made in these patients and in the experimental animals support the proposition that mechanical stimulation of the heart offers an immediate, simple, and effective method of cardiac resuscitation during standstill. This method is recommended as a routine measure to reestablish automaticity or to maintain cardiac activity; while other methods, such as electrical stimulation or the administration of certain pressor amines, are being prepared, blows to the precordium ("fair on the breastbone"), combined, when indicated, with mouth-to-mouth breathing,

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The place of publication of the periodical appears in brackets preceding each abstract.

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superficial phlebitis has been far from satisfactory. Of the last five such patients seen at the vascular clinics of the Hospital of the University of Pennsylvania and of the Bryn Mawr Hospital, one responded to treatment but the other four soon required hospitalization for anticoagulant therapy.

In short, I believe that phenylbutazone may be of benefit in some patients with superficial phlebitis, but I cannot agree that "the advent of phenylbutazone in the treatment of thrombophlebitis offers much help in controlling" the disease.

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A PLEA FOR PITY IN PUBLISHING PERCENTAGES

To the Editor:—To know is to foresee and to write is to teach; to give percentages in a medical paper is to do all of these. When one reads that "of 16 patients with carcinoma of the pancreas 6.3% exhibited bone metastases" one expects 6.3% of the next 100 patients with carcinoma of the pancreas to exhibit the same phenomenon; this is what the author must have meant. From his 16 patients he knows what will happen to the next 100 (this is what the term per centum implies; it is a forecast), and he goes out of his way to save his reader the trouble of figuring. The reader is actually being uncooperative by doing the calculations again to find that 6.3% of 16 patients is one patient.

The author may want to help the reader make comparisons by saying that the x-ray examination was correct in 60% of five patients with polyposis of the stomach and the gastroscopic examination in the same group was correct in 80% of five patients and that x-ray examination was conclusive, however, in only 22.2% of nine patients who, at operation, did not reveal any lesions in the stomach. Obviously 60% and 80% appear more meaningful than three of five and four of five; certainly 60% and 22.2% can be more easily compared than three of five and two of nine. They differ by 37.8%—or is it 270.27%? (How does one properly compare percentages? Does one subtract them? Does one divide them? If so, which one into which one?)

At times, the reader is close to losing his cheerfulness about finding facts among flowery figures and may feel like sitting down and crying. He is apt to feel this way when reading percentages referring to multiple subgroups: "The choledochus was explored in 53.4% of the women and in 63% of the men; stones were found during choledochal exploration in 38.4% of the women and in 57.3% of the men." Does this statement mean 38.4% of all the women included in the study or 38.4% of the 53.4% of women whose choledochus was explored? The statement could not have been written for those who do not care, and those who do are anxious to know.

If my son were to ask me for just one suggestion before writing a medical paper, I should warn him about asking for advice and getting some that is hard to refuse and not easy to use and then I should tell him: "Always give the absolute figures when you mention percentages. Do not worry about being redundant." For instance: "Forty-one of the 115 patients were living and 74 were dead. . . . Bleeding from esophageal varices had occurred in 33 (28.6%) There were 20 (17.3%) who died of exsanguinatio 31 (25%) who died of hepatic failure, and 23 (20% whose death was due to unrelated causes." If h should insist on just one more suggestion, I shoul add: "In clinical articles avoid giving fractions c 1%. They clutter your paper; they make you figures harder to grasp and harder to remembe they tend to reflect pedantry rather than precisio and they cannot matter."

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P.S. References to quotations given herein will b *supplied on written request.*

SUPPLY OF PHYSICIANS

To the Editor:—In the front of The Journa Dec. 5, 1959, was a card asking for contributions t medical schools. In the same issue there was a article telling of the great present shortage of ph sicians and the increasing future shortages.

I do not believe that there is a lack of physician My local paper reported that one physician ha performed 10 tonsillectomies in one family. A item in *Medical Economics* tells of a pediatricia spending much of his time weighing and examinin well babies. In many hospitals a number of useles operations are done every day; for instance, sus pension of uteri, many exploratory operations tubal ligations, and removal of every questionable chronically inflamed appendix.

I believe that, if more doctors would devot themselves to the care of the sick, their pocketbook might not bulge so much but the cry for mor doctors would abate.

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It is suggested that the Bane Report, mentioned in an editorial in this issue, be read.—Ed.

administered intravenously to the patients, one of whom received 110 cc. and the other 120 cc. of the solution. The improvement was prompt and progressive, as evidenced in the serum electrolyte concentrations, quinidine plasma concentrations, blood pressure, and electrocardiograms. The remainder of the patients' hospital stay was uneventful.

Death in Asthmatics. B. S. Cardell and R. S. B. Pearson. Thorax 14:341-352 (Dec.) 1959 [London].

The authors use the term "asthma" to signify a symptom complex characterized by attacks of dyspnea, associated with widespread expiratory wheezing rhonchi. This study is based on the findings in 68 fatal cases of asthma, most of the patients in question having been observed by one of the authors for many years. Death was considered, on clinical grounds, to be related directly or indirectly to the asthmatic state in all these patients, and the asthma seemed to be primary in all but 16, in whom it developed secondary to bronchitis. The pathological aspects of asthma were studied in the 31 patients on whom autopsies were performed. The entire group included 35 males and 33 females. In cases of primary asthma, female deaths exceeded male deaths up to the age of 40 years (14 females and 9 males), but after that age, the number of deaths were about equal in the 2 sexes (14 males and 15 females). In deaths from asthma secondary to bronchitis, males exceeded females (13 and 3 respectively).

Analysis of the precipitating factors showed that allergic factors were present in 24 of the 44 cases beginning before the age of 40 years but in only 2 of the 24 cases beginning later. Infection was the commonest factor encountered, and its incidence increased with age; it was recognized in 34 of the 44 cases beginning before the age of 40 and in 21 of the 24 cases beginning later. Psychological precipitating factors were found in 13 and 7 cases, respectively, in the 2 age groups.

There were 11 patients (6 males and 5 females) in whom the asthma was associated with flexural eczema and in most of them also with rhinorrhea. Allergic sensitivities were present in 8 patients; in this group the asthma was considered to be primarily allergic in origin, but infective episodes were present in 7. Nine of the 11 patients died in status asthmaticus, one of anaphylaxis some seconds after a desensitizing injection of pollen, and one with cor pulmonale. The "pollen group" of patients included 8, all of whom had a long history of asthma or hay fever, or both, and gave positive skin reaction to pollen; 5 of them died in the summer months.

In a group of 4 patients in whom allergic sensitivity was judged to have played an important part at some stage of the illness, all were sensitive to common inhalants. Three of the 4 patients died in status asthmaticus, and one in anaphylactic shock, after an injection of Pyelectan for renal tract investigation. Status asthmaticus caused death also in all 6 patients of the psychological group, in whom overwhelming emotional factors were present. In the 13 patients of the infective group the histories indicated that attacks of asthma antedated infective symptoms; bronchitis or lung infections were superimposed on preexisting asthma in contrast to the 16 patients of the bronchitic group, in whom asthma developed secondary to respiratory tract infections. Nine of the 13 patients died in status asthmaticus or of acute attacks of asthma. In 10 patients of an "intermediate group" no clear indication was found as to the predominating factor. All died in status asthmaticus or of acute attacks of asthma.

Of the pathological findings in the lungs in deaths due to asthma, 3 are especially important: mucous plugging of bronchi and, in the bronchial wall, infiltration by eosinophil leukocytes and a thickened basement membrane. Together, these features are diagnostic of severe active asthma. Obstruction of the bronchial lumen by mucous plugs is now generally regarded as the main factor impairing pulmonary ventilation in these cases, though spasm of the bronchial muscle and congestion of the bronchial wall may help to reduce the airway. The degree to which bronchi are plugged with mucus varies from case to case. In general, the more damaged the lungs are as a result of past infection, the less the degree of mucous plugging required to cause death.

The Use of Prednisone to Initiate or Potentiate Diuresis in Chronic Hepatic Disease with Ascites. J. V. Carbone and H. B. Matthews. Gastroenterology 38:52-59 (Jan.) 1960 [Baltimore].

The authors studied the effect of prednisone in 12 patients, 3 of whom were women with ascites associated with chronic hepatic disease. One patient had a chronic viral hepatitis, 1 had a secondary biliary cirrhosis, and 10 had portal cirrhosis. The patients received either prednisone, chlorothiazide, or meralluride alone, or a combination of prednisone and one of the diuretics. If diuresis did not occur, the refractory patients were given all 3 drugs. The dosage schedule was as follows: prednisone, 20 or 40 mg. orally, in 4 divided doses daily; chlorothiazide, 500 mg. orally, in 4 doses daily; meralluride, 2 ml. by intramuscular injection at varying intervals.

Of the 4 patients who received prednisone alone, 2 responded with vigorous natruresis and diuresis and 2 with mild natruresis and negligible weight loss. Prednisone alone or either of the 2 diuretics alone did not induce diuresis in 5 patients; however, the combination of prednisone and chlorothiazide or meralluride resulted in vigorous diuresis. The 3 patients who had proved refractory to prednisone alone and to either combination of diuretic agent may successfully maintain life. In the first 3 patients life appeared to have been significantly prolonged by the simple expediency of thumping. Blows to the precordium should be tried even if ventricular fibrillation is suspected. Not only may ventricular fibrillation be confused with multiple variform ventricular extrasystoles in the electrocardiogram, but it may also be followed by standstill.

Thumping of the precordium succeeds in preserving life by evoking ectopic beats which may reawaken cardiac automatism. In the normal heart mechanical stimulation elicits a single response. In the altered, damaged, or hypoxic myocardium a blow may produce a multiple response manifested by a tachycardia or even fibrillation. Experimentally, a prolonged ectopic tachycardia follows mechanical stimulation under the influence of a variety of substances but particularly in the presence of calcium deprivation. This effect is best explained by the formation of oscillatory after-potentials occurring in the wake of a single depolarization.

Chronic Idiopathic Pericardial Effusion with Special Reference to the Development of Constrictive Pericarditis. J. Scheuer. Circulation 21:41-48 (Jan.) 1960 [New York].

Constrictive pericarditis is usually found to be a sequel of tuberculosis, of other pyogenic infections, of trauma with hemopericardium, or of neoplasm; chronic idiopathic pericardial effusion, however, is not, as a rule, considered as a possible precursor. The author presents a case of chronic idiopathic pericardial effusion in a middle-aged hypertensive woman. The findings and course of 18 similar cases are reviewed. The course is unpredictable. Some patients will be asymptomatic, but in a significant percentage adhesive or constrictive pericarditis will develop, and others will have chronic tamponade with hepatosplenomegaly and ascites. It is concluded that, since the course cannot be predicted, and since surgery provides a maximum therapeutic result when performed in the early stages, these patients should have a pericardiectomy when the condition is discovered.

Hemodynamic and Hypotensive Effects of Long-term Therapy with Chlorothiazide. J. Conway and P. Lauwers. Circulation 21:21-27 (Jan.) 1960 [New York].

The over-all effectiveness of long-term therapy with chlorothiazide and the hemodynamic mechanism by which this treatment reduces the blood pressure were investigated. After investigation of the cardiac and renal status, 83 unselected ambulatory patients with hypertension were given chlorothiazide as the sole hypotensive medication. None of these patients was edematous, but 16 previously had undergone splanchnicectomy without reduction in the blood pressure. The usual maintenance dose of chlorothiazide was 0.5 Gm. twice daily after an initial 3-day period of 1 Gm. twice daily. In 5 patients a larger dose of 2 Gm. per day was administered continuously. Patients were urged to reduce sodium intake by avoiding salty foods and by eliminating salt from cooking and at the table. Blood pressure readings were taken twice daily. Treatment was maintained for at least one month in all except 7 subjects, who had not responded after 2 weeks and whose clinical condition required the use of more potent drugs. At varying periods after the first month of treatment the remaining patients who failed to respond were withdrawn from the investigation to be given other drugs. The average duration of therapy for the entire group was 5.4 months.

A significant fall in blood pressure was found to occur in 66% of the patients; the average reduction in pressure in patients with essential hypertension was 26/17 mm. Hg. After 1 or 2 weeks of therapy, the plasma volume and cardiac output fell, and total peripheral resistance increased. After one month or more of continued treatment, the plasma volume and cardiac output were restored to pretreatment levels, while the fall in blood pressure was maintained. Long-term therapy has, therefore, produced an action on the peripheral vessels leading to a reduction in total vascular resistance.

Cardiotoxic Effects of Quinidine and Their Treatment: Review and Case Reports. D. J. Bailey Jr. A. M. A. Arch. Int. Med. **105**:13-22 (Jan.) 1960 [Chicago].

Molar sodium lactate was successfully used to reverse severe cardiac depression which developed in 2 patients after the administration of quinidine. A woman, 80 years old, was hospitalized because of an acute myocardial infarction. The other patient, a woman, 43 years of age, was hospitalized with a history of sudden collapse, followed by difficulty in speech and weakness of the left arm and leg. The neurological symptoms cleared considerably within 4 hospital days. However, cardiac decompensation persisted in both patients, and an attempt at conversion to the normal sinus rhythm by the use of quinidine was begun. Two hundred milligrams of quinidine sulfate was given every 2 hours for 6 doses on the first day to both patients; the dose was increased to 300 mg. in one patient and to 400 mg. in the other on the second day. Electrocardiograms revealed persistent atrial fibrillation, with no changes characteristic of quinidine effect, in the younger patient 2 hours after the last dose (400 mg.) on the second day of drug treatment. The next morning quinidine was not given, because the patient began to complain of generalized weakness, abdominal pain, and increasing dyspnea. The electrocardiogram of the older patient revealed evidence of quinidine intoxication on the second day of drug therapy. Molar sodium lactate was then heavy chronic staphylococcic skin infections were present on a medical ward. The second, or respiratory, phase began when Asian influenza appeared in the hospital. Within a short time many cases of staphylococcic pneumonia appeared in the same area. As influenza disappeared, the epidemic strain spread throughout the hospital, causing mostly skin disease. The pattern of spread has been reported to follow the movement of heavily contaminated patients in the hospital. In this outbreak asymptomatic carriers were shown to be unimportant factors in spreading infection. An episode of spread into the community is documented in a family that suffered 2 deaths from staphylococcic pneumonia and 3 nonfatal staphylococcic infections. Evidence suggests that the 52/52A/80 strain may be a particularly dangerous one. In the epidemic studied, morbidity and mortality were high, and infections occurred despite careful control measures. Resistance to antibiotics developed rapidly, and asymptomatic carriers tended eventually to acquire clinical disease.

A Case of Mondor's Disease. W. van Enst and H. de Jager. Arch. chir. neerl. 11:393-398 (no. 4) 1959 (In English) [Arnhem, Netherlands].

The case of a woman, 31 years of age, with the form of thrombophlebitis known as Mondor's disease is described. This entirely benign condition should be known in order to prevent confusion with carcinomatous lymphangitis. The condition consists of transformation of one of the veins of the thoracic wall, particularly the lateral thoracic, the thoracoepigastric, or the superior epigastric vein, into a firm cord-like strand. This transformation is sometimes associated with painful sensations. There are no general signs of inflammation. The blood picture in the patient observed by the authors could be considered normal, with the exception of mild eosinophilia (5%). The erythrocyte sedimentation rate was 4-11, the leukocyte count was 4,000 per cubic millimeter, and the hemoglobin concentration was 14.6 Gm. per 100 cc. As a rule, the condition, as happened in the case reported here, disappears spontaneously within a few weeks or months and requires no treatment. In the majority of cases, a biopsy is unnecessary. Attention is drawn to differences in microscopy from the well-known types of thrombophlebitis occurring elsewhere in the body.

SURGERY

Spontaneous Rupture of the Esophagus. R. D. Mahon Jr. and L. J. Robison. Am. Surgeon 26:24-29 (Jan.) 1960 [Baltimore].

Since Boerhaave first described spontaneous rupture of the esophagus in 1724, some 200 cases of this condition have been reported, with some 50 survivals. All the patients cured, save one, had surgical intervention of some sort. The lowest mortality rate was in patients subjected to thoracotomy with repair of the esophagus. Failure to make the diagnosis of esophageal rupture is due to failure to consider it. One should always think of it in patients with severe epigastric or chest pain after vomiting, in patients with both abdominal and chest findings, in patients thought to have perforated peptic ulcer, in patients with cervical emphysema, in patients who are in a shock-like state after vomiting, and in patients with hydropneumothorax. The diagnosis may be confirmed by the demonstration of esophageal leak after swallowing radiopaque material. Early diagnosis, followed by thoracotomy, repair of the esophagus, and pleural drainage, may be expected to give a favorable outlook in a condition almost uniformly fatal otherwise.

The authors report on a 60-year-old man with spontaneous rupture of the apparently normal esophagus, who was admitted to the East Dallas Hospital in Dallas, Texas, in severe distress. Severe, cramping, upper abdominal pain with interscapular radiation had started after eating Sunday dinner, followed by vomiting twice. The patient was thought to have a perforated ulcer. Laparotomy was performed, and careful abdominal exploration was negative except for an esophageal hiatus enlarged to 5 cm.; on opening the peritoneum at the hiatus, one entered a large mediastinal collection of content of a recent meal. A rent in the lower esophagus was palpated. The chest was opened, and by extending the incision through the 7th intercostal space as far as the anterior axillary line, a 3-cm. longitudinal rupture of the left anterolateral aspect of the esophagus was found. The esophagus was repaired with 2 layers of interrupted fine cotton. Early primary repair of the esophagus thus was effected after incorrect preoperative diagnosis, and recovery was established, despite dehiscence of the thoracoabdominal incision. Whenever abdominal exploration for suspected perforated peptic ulcer is negative, the possibility of esophageal rupture should be considered. Immediate steps should be taken to ascertain its presence, and, most importantly, chest roentgenograms should be obtained, with swallow or instillation of radiopaque fluid.

Thromboendarterectomy for Coronary Artery Disease. C. P. Bailey, D. P. Morse and W. M. Lemmon. Am. J. Cardiol. 5:3-13 (Jan.) 1960 [New York].

The authors report on 13 men, between the ages of 37 and 57 years, and on 2 women, aged 28 and 35 years, with coronary arterial disease, in whom endarterectomy or thromboendarterectomy was attempted in several hospitals in Philadelphia. Of the 15 patients, the left main and anterior descending coronary arteries were operated on in 3, the anterior descending coronary artery alone in 5, the left cir-

and steroid also failed to respond to administration of prednisone plus both diuretics. In the 4 patients who responded to prednisone alone, serum potassium and sodium values were normal. These patients, however, showed higher serum albumin levels than the patients in the other 2 groups. Since the serum bilirubin values were significantly higher in the 3 patients who responded to prednisone alone than in the 3 patients who were refractory to all the drugs, the elevated serum bilirubin levels apparently did not affect the response. Two patients developed hepatocerebral coma while receiving prednisone and chlorothiazide, necessitating discontinuance of the drug therapy.

Prednisone has thus been shown to induce diuresis and natruresis and to potentiate the action of diuretic agents in this series. The diuretic action of prednisone appears to be independent of improvement in liver function and to be related primarily to alterations in renal function induced by the adrenal steroids.

Cardiac Changes in the Course of Leukemia. J. Popescu, V. Enescu and P. Grozea. Helvet. med. acta 26:860-875 (Dec.) 1959 (In German) [Basel, Switzerland].

The authors report on 102 patients, 60 with chronic and 42 with acute leukemia, who were studied for cardiac changes occurring in the course of their disease at the Colentina Hospital, in Bucharest, Romania. Of these patients, clinical signs of involvement of the heart were observed in 12.5%, electrocardiographic changes in 35%, and anatomicopathological alterations in 42.5%. In the patients with clinical cardiac symptoms, the leukemic myopericardial alterations either caused focal damage due to coronary insufficiency or caused other forms of cardiac insufficiency; hypodiastolic insufficiency (insufficiency of the right heart) was observed in one patient with leukemic myopericardial infiltration associated with a primary mesothelioma of the pericardium; cardiac insufficiency was observed in another patient with an acute bout of chronic granulocytic (myeloid) leukemia with massive myocardial infiltrations based on previously existing sclerotic changes of the myocardium. The electrocardiographic changes varied. In many patients, disturbances of rhythm and of conduction, as well as ischemic phenomena, occurred simultaneously. A parallel between these anomalies and the considerable myopericardial damage did not, however, exist.

The anatomicopathological damage was of most varied nature, ranging from massive leukemic myopericardial infiltrations with degeneration of the muscle fibers to a necrosis of these infiltrations and the occurrence of secondary infected thrombi in the capillaries of the myocardium. The myocardial fibers showed cloudy swelling and granular or vacuolar dystrophy, with disappearance of the striations or fragmentations of the fibers, particularly in the neighborhood of the infiltrations. With the exception of 3 intracavitary leukemic thrombi (in the right atrium, in the right ventricle, and in the left atrium, respectively), no valvular or endocardial changes were found. The pericardium was involved in the infiltrative process in 6 patients, 5 of whom had acute leukemia.

Serum "Trypsin" (or Arginine Exopeptidase) Screening Test for Cancer of the Pancreas. G. L. Nardi. Gastroenterology 38:50-51 (Jan.) 1960 [Baltimore].

The author studied the diagnostic usefulness of the serum trypsin test in 10 patients with carcinoma of the pancreas; the average trypsin value was 379 units, the highest value being 580 units and the lowest value 170. Control determinations of the serum trypsin value were also made in 37 healthy adult volunteers and in 27 hospitalized patients who had no evidence of pancreatic disease; the average trypsin value was 30 units. Since the standard error of the method was found to be ± 50 units, the author arbitrarily set 100 units as the maximal normal value. The correct preoperative diagnosis of carcinoma of the pancreas was made clinically in 7 patients. The erroneous preoperative diagnoses in the remaining 3 patients were, respectively, abdominal aortic aneurysm, metastatic carcinoma, and sprue syndrome. The findings of the author suggest that in the presence of pancreatic disease there is a significant elevation of the serum trypsin, or arginine exopeptidase, level. The elevation is believed to result from obstruction in the ductal or acinar system of the pancreas, combined with an actively secreting gland. The serum trypsin determination proved to be a more sensitive and reliable index of pancreatic disease in these patients than either the serum amylase or the serum lipase test. The serum trypsin test, therefore, is a useful laboratory aid in the diagnosis of carcinoma of the pancreas.

The Genesis and Spread of a Hospital Staphylococcal Epidemic on an Adult Medical Ward. R. A. Vogel, Y. J. Trotter, J. H. Shinaberger and J. E. McCroan. New England J. Med. 261:1301-1309 (Dec. 24) 1959 [Boston].

A severe outbreak of staphylococcic disease at the Veterans Administration Hospital in Atlanta, Ga., is described. Because it began during a period of routine bacteriophage typing of staphylococci, its entire course was thoroughly documented. All 63 cases were caused by Staphylococcus aureus, type 52/52A/80, which had previously been uncommon in the hospital. There were 14 deaths related directly or indirectly to the epidemic strain. The outbreak consisted of 3 distinct phases. During the first, or preepidemic, phase 3 patients with to 12 weeks of intensive ambulatory and hospital treatment with drugs, physical therapy, extension, or fixation by corset, and if, in addition, the patient is unable to work during this period, surgical treatment should be considered. Operation should be advised in the presence of definite monoradicular manifestations of abolition or decrease in function. In rare cases of pain, refractory to opiates, surgical treatment may be performed without much delay, and patients with massive prolapse of an intervertebral disk resulting in symptoms of transverse myelitis should be operated on within the first 12 hours, provided that exact localization of the level is possible.

Coarctation of the Aorta in Infants: A Clinical and Experimental Study. T. H. Burford, T. B. Ferguson, D. Goldring and M. Remsen Behrer. J. Thoracic & Cardiovasc. Surg. 39:47-59 (Jan.) 1960 [St. Louis].

The authors present observations on 16 infants with coarctation of the aorta and patent ductus arteriosus, who were subjected to early surgical treatment. The median age of the patients at the time of the operation was 6 weeks. There was great anatomic variation in the relationship of the 2 lesions. Clinically, all the infants were in refractory cardiac failure, and they had marked cardiomegaly. The electrocardiographic pattern varied. The diagnosis was made by demonstrating a significant pressure gradient. Seven of the infants died during operation, but there were only 2 deaths among the last 11 children operated on. There was one late death. The other 8 children who survived the operation have been followed for an average of 2 years. All are free from symptoms, but several have additional intracardiac shunts, which will have to be closed in the future. On the basis of their observations on these infants, the authors have become convinced that prompt correction of the coarctation and division of the ductus represent the only rational treatment. They cite evidence to the effect that coarctation and patent ductus are also a lethal combination in experimental animals.

Problems of the Surgical Management of Coarctation of the Aorta. L. K. Groves and D. B. Effler. J. Thoracic & Cardiovasc. Surg. 39:60-90 (Jan.) 1960 [St. Louis].

The authors discuss problems that have continued to perplex them in the course of surgical treatment of 60 patients with coarctation of the aorta. The problems have recurred with significant regularity. The primary aim was to clarify, rather than to solve, the problems under discussion, but the research involved in assembling data has led to some tentative conclusions. Thus, an aggressive surgical approach is indicated in infants with aortic coarctation and congestive heart failure. While in many of these infants the coarctation is only part of a complex cardiac anomaly, the coarctation and the frequently associated patent ductus are the most accessible lesions from the surgical standpoint, and their correction has had gratifying results. Residual aortic hypoplasia seems to be well tolerated. No conclusions can be drawn about the surgical treatment of coarctation in patients over 45 years of age. The surgical risk is high, and each case must be judged on its own merits.

While their observations on the postcoarctation abdominal pain syndrome is limited, the authors gained the impression that this complication is probably associated with extremely complete correction of coarctation and maximal increase in visceral circulation. They hope that additional reports of treatment with antihypertensive drugs will be forthcoming. They believe that a strong case can be made for moderate residual anastomotic narrowing. It seems reasonable to avoid the use of grafts if an anastomotic lumen, 1 cm. in diameter, can be accomplished without their use. Postoperatively, these patients tend to have a labile blood pressure, and it is thus difficult to ascertain which ones are truly hypertensive; in this series, the figure approximates 10%. Study of such patients suggests that the hypertension is due to a small inelastic central arterial reservoir, rather than to residual obstruction, and that, in all probability, the same factors play a role in the hypertension of the untreated patient.

Pericardiectomy for Relapsing Pericarditis and Chronic Constrictive Pericarditis. W. S. Blakemore, H. F. Zinsser, C. K. Kirby and others. J. Thoracic & Cardiovas. Surg. 39:26-34 (Jan.) 1960 [St. Louis].

The authors present for consideration the suggestion to remove the diseased pericardium before the scar contracts to the extent of reducing the efficiency of the cardiac mechanism. This is not proposed as a treatment for patients with acute pericarditis, but rather for those in whom the relapsing character of the disease has been established in the absence of cardiac constriction or tamponade. The authors review observations on 28 patients with chronic constrictive pericarditis and on 8 with recurrent nonconstrictive pericarditis, all of whom were subjected to pericardiectomy.

A relapsing character of the disease was a prominent feature in a few of the many patients with acute pericarditis. These patients had had an acute illness, usually easily diagnosed as pericarditis and associated with pleuritis and slight pleural effusion. After symptomatic nonspecific treatment, the patients appeared to have made a good recovery when the process was rekindled by physical exertion. Chest pain, malaise, fever, pericardial friction rub, changes in the electrocardiogram, leukocytosis, anemia, increase in the sedimentation rate, and reversal of the serum albumin-globulin ratio were commonly found. Progressive changes in the cardiac cumflex and anterior descending coronary arteries in 2, the left circumflex, anterior descending, main and right coronary arteries in 2, and the right coronary artery only in 3. Thirteen patients survived the operation, and one of these, in whom only the anterior descending coronary artery was treated, died of an acute occlusion of the right coronary artery 8 months after a seemingly successful surgical intervention. Of the remaining 12 patients, the condition of one was unchanged, 3 were slightly improved (fair results), 4 were moderately improved (good results), and 4 were markedly improved (excellent results). The experience with the patient who died after 8 months convinced the authors that all affected branches of both coronary arteries should be relieved of their obstructing lesions at the time of the original intervention.

These results indicate that coronary thromboendarterectomy is technically possible, with excellent results, in properly selected patients. Ideally, one should prefer a relatively young and vigorous person with a well-marked anginal syndrome but without significant complication and without a history of myocardial infarction or electrocardiographic evidence of the same. One might also accept a similarly vigorous person who has suffered from but one attack of myocardial infarction but who continues to have anginal pain on effort, or perhaps after the elapse of months or years has a recurrence of typical anginal pain on effort. In this type of patient it is essential that the heart should not be enlarged significantly and that heart failure should not be present. Patients with a definite history of 2 or more bouts of infarction would represent significantly less desirable candidates for surgical intervention. One might establish the age of 60 years as the upper limit of permissible operability, and one might refuse surgical treatment to any patient in frank heart failure or one with cardiac enlargement more than grade 2 plus.

Coronary thromboendarterectomy is the only operation so far performed for coronary arterial disease which directly attacks and attempts to remove the pathological condition. While long-term evaluation of the patients remains to be determined, the operative results to date have been encouraging, and further trial of the procedure would seem to be indicated. The value of coronary angiography preoperatively is emphasized.

Experimental Evaluation of Grafts in the Canine Inferior Vena Cava. H. A. Collins, G. Burrus, and M. E. DeBakey. Am. J. Surg. 99:40-44 (Jan.) 1960 [New York].

The feasibility of replacing the canine inferior vena cava with autogenous peritoneal tubes, Dacron grafts, and autogenous aorta was assessed. In another group of dogs that served as controls, a segment of the inferior vena cava was excised; the segment was reversed in direction, and then anastomosed to the proximal and distal ends of the vena cava. Regardless of the type of graft employed, thrombosis always occurred within 4 months. No form of graft demonstrated clear superiority over the others. Thrombosis of the grafts appears to be due to occlusion by perivascular scar tissue. Venous flow and pressure appear to be of greater significance in determining continued patency of a venous graft than the type of graft employed.

Experiences with Conservative and Surgical Treatment of Prolapse of Lumbar Intervertebral Disk. W. Burkart. Chirurg 30:540-543 (Dec.) 1959 (In German) [Berlin].

The author reports on 258 of 350 patients with prolapse of a lumbar intervertebral disk, who were operated on in the surgical department of the Veronika Clinic in Stuttgart, Germany. Of the 258 patients, 64 were operated on between 1949 and 1952; 88, between 1952 and 1954; and 106, between 1955 and 1958. Fenestration of the ligamenta flava, according to Love's technique, was the surgical procedure of choice; it was performed with the patient under local anesthesia with 70 to 100 cc. of a 1% solution of procaine hydrochloride and epinephrine. In the last 2 years before the operation the patients had not been able to work for an average period of 6 months. The work capacity was restored within an average period of 2.4 months after the operation. Of the 258 patients, 90.3% were satisfied with the results of the operation, and 2.4% were improved and able to work; 19 patients (7.3%) were not satisfied with the results of the operation, but 16 of them later on became able to work again. The degeneration of the intervertebral disk, as such, and the more or less strong reactive changes in the bones, and the small joints could not be favorably influenced by the Love operation, and that explains why some of the patients still had pain in the sacral region after the operation. These pains, however, were tolerated much better by the patients than acute sciatic pain. Of the 106 patients operated on in recent years, 56 were completely free of pain, 10 had temporary complaints (6 to 12 months postoperatively), and 25 had permanent mild pain, and 10 permanent moderate pain in the sacral region; a hypesthesic dermatoma occurred in 3 patients, and preoperative paresis persisted postoperatively in 2.

The success of conservative treatment of prolapse of an intervertebral disk cannot be asserted statistically. In the course of years the author adopted the following program of conservative and surgical management, which has proved successful in patients with dorsolateral prolapse of an intervertebral disk, and, herewith, in the treatment of sciatic pain: If a permanent success does not result from 8 ies. With open thoracotomy one can extend the diagnosis to about 90% of the patients with pleural effusion.

Pericardial effusion presents the same challenge and basically the same diagnostic approach as that of pleural effusion. The authors performed pericardial biopsy in 4 male and in 5 female patients, between the ages of 11 and 53 years, with a clinical diagnosis of pericardial effusion; all had signs of chronic tamponade. A final diagnosis of myocarditis was made in 2 of the 9 patients, of chronic pericarditis in 6, and of lymphopericardium in 1. One patient, an 11-year-old girl, died. All but one of the patients had the anterior two-thirds of the pericardium removed. The one patient who was the exception had a small pericardial window with subsequent pericardiectomy. There were no complications in this group. It is apparent that a nonspecific pericarditis with effusion exists and must be considered in all patients in whom the pericardial effusion does not clear. A biopsy should be obtained from patients with so-called chronic tamponade due to pericardial effusion, and if the presence of constriction of either the epicardium or the pericardium is observed, it should be removed. If chronic pericardial effusion is present, a pericardiectomy should be performed. The use of a pericardial window, which will soon seal and be obstructed by the lung adhering to the surface, should be discontinued. In certain cases of myocarditis it may be necessary to do an exploration to rule out the presence of constriction or chronic effusion.

An Experimental Study of Resection and Replacement of the Superior Vena Cava. W. M. East and W. H. Muller Jr. Am. J. Surg. 99:6-12 (Jan.) 1960 [New York].

A study of the literature on the treatment of obstruction of the superior vena cava revealed to the authors that the problem of replacement of the large veins has not been completely solved. The most ideal replacement of the superior vena cava would seem to be an autogenous vein graft, but large autogenous veins are difficult to obtain. The authors present an experimental study of methods for replacing the vena cava with prostheses. Experiments were performed on 14 dogs, nylon and Teflon prostheses being used for replacement. Nylon prostheses were implanted in 7 dogs, 2 of which had undergone partial occlusion of the superior vena cava. Teflon tubes were used for replacement of the superior vena cava in 7 animals, one of which had undergone partial ligation of the superior vena cava and transection of the azygos vein. The Teflon prostheses showed excellent results in 7 dogs followed up to 6 months. Superior vena cava prostheses of nylon in the other 7 dogs were less successful, as shown by autopsy, with narrowing in all the prostheses. Only one animal in this group had complete occlusion by thrombus; in the remaining 6 there was no clinical evidence of obstruction, and venous pressures remained normal postoperatively.

These studies indicate that a semirigid tube is the chief requirement for a superior venal caval prosthesis. Teflon grafts were superior to nylon grafts, because fibroplastic response and thrombus formation were much less. It is suggested that crimped Teflon vascular prostheses might be suitable in clinical application for segmental replacement of the obstructed superior vena cava.

Retroperitoneal Non-chromaffin Paraganglioma. R. T. Sessions and H. W. Scott Jr. Am. J. Surg. 99: 70-75 (Jan.) 1960 [New York].

Nonchromaffin paraganglioma is the term applied to tumors which are histologically similar to tumors of the carotid body but which occur in regions of the body other than the head and neck. These are rare tumors which are morphologically similar to tumors of the chemoreceptor system but which are more frequently malignant. The authors present the clinical history of a 17-year-old student who had a retroperitoneal nonchromaffin paraganglioma. The tumor had not responded to radiation and had invaded the vena cava and aorta.

Complete excision of the extremely vascular tumor could be effected only by en bloc removal of the tumor with the involved segments of the lower abdominal aorta, inferior vena cava, and right kidney. After mobilizing the tumor laterally, the aorta and vena cava were clamped and transected above and below the tumor. The inferior mesenteric artery and lumbar vessels were divided, and, with the specimen elevated, the upper portion of the tumor was dissected off the posterior aspect of the aorta from the diaphragm downward. The tumor was dissected off a short segment of the left renal artery posteriorly. However, because of complete encasement of the right renal pedicle by tumor, these vessels were sacrificed, and the right kidney was removed. Two lyophilized thoracic aortic homografts were reconstituted, and 12-cm. segments of graft were used to restore the continuity of the aorta and the vena cava. Twenty months after operation the grafts were demonstrated to be patent, and there was no clinical evidence of recurrence of the tumor. This case apparently represents the second recorded instance in which a graft interpolated into the inferior vena cava has continued to function for a prolonged period.

Mesenteric Cysts. N. F. Sprague Jr. Am. Surgeon 26:42-49 (Jan.) 1960 [Baltimore].

The author reports on a 44-year-old man and a 25-year-old woman with mesenteric cysts, who were seen at St. Vincent's Hospital in Los Angeles. Their cases were the only ones of this kind seen at this silhouette were noted by roentgenographic examinations. Repeated hospitalizations were required, and the patient approached cardiac invalidism. The process was arrested by bed rest and medical therapy.

Prior to recognizing the typical course of the pericarditis, there was reluctance to recommend surgery for these patients. The disease was reactivated when they returned to their normal activity. Only 2 of the 8 patients with *recurrent nonconstrictive* pericarditis were able to work during any part of the time after onset of their symptoms. Cardiac constriction or tamponade in a mild form was noted *in only one* of these patients during a late phase and prior to the authors' recommending early surgical removal of the pericardium, which was not overtly interfering with the cardiac function.

Among the 28 patients with chronic constrictive pericarditis who were subjected to pericardiectomy, there were 3 operative deaths. These deaths occurred in patients with long-standing heart failure. There were no operative deaths among the 8 patients with relapsing pericarditis, in whom operation proved easier and the morbidity was considerably less. Pericardiectomy and decortication of the heart *should be carried out before the patient becomes* a poor surgical risk, because of deterioration associated with cardiac constriction, and during the time when surgical removal of the pericardium is an easier procedure. The pericardium in patients with tuberculosis or idiopathic pericarditis and pericardial effusion should be removed without waiting for the development of constrictive pericarditis.

The Results of Surgical Correction of Atrial Septal Defect Complicated by Pulmonary Hypertension.

H. V. Liddle, B. W. Meyer and J. C. Jones. J. Thoracic & Cardiovas. Surg. 39:35-46 (Jan.) 1960 [St. Louis].

In the presence of atrial septal defects of the secundum type, there is little flow across the defect at birth, but as the systemic resistance increases, a left-to-right shunt develops, which gradually becomes larger, so that the pulmonary flow is 2 or 3 times as extensive as the systemic flow. To accommodate this volume of blood, the pulmonary vessels dilate, and the right ventricle becomes overloaded and also becomes dilated. The electrocardiogram reflects this dilation as delayed conduction. Prolonged exposure to excessive flow is occasionally associated with morphologic changes in the pulmonary vessels, resulting in pulmonary hypertension and eventually in a reduction of the volume of the shunt. Even with a reduction of the shunt, the work of the right heart increases as the pulmonary resistance increases, and closure of an atrial septal defect, complicated by severe pulmonary vascular resistance, is often associated with acute right ventricular dilatation, fibrillation, and death. Thus, selection of patients with severe pulmonary hypertension who will tolerate closure of the defect is difficult, and evaluation of pulmonary artery pressure alone is not a sufficient criterion.

In the department of surgery of the University of Southern California, Los Angeles, simple atrial septal defects of the secundum type were treated surgically in 180 patients. Among these, there were 15 patients, all adults, whose defects were complicated by pulmonary artery pressures in excess of 50 mm. Hg, which the authors regard as hypertensive. Five of the 15 patients succumbed at operation, and 2 were not benefited by closure of the defect. Four clinical and laboratory observations were related to the surgical failure in these 7 patients, namely, cyanosis, congestive heart failure, severe right ventricular hypertrophy, and a marked discrepancy in vessel size in roentgenologic studies. When 2 or more of these observations are made in a patient, there probably exist irreversible pulmonary vascular changes. The poor results of surgery in this group of patients, compared with those in the uncomplicated atrial defect group, are evidence that these defects should be closed when they are recognized. There is nothing to be gained by *procrastinating.*

Pleural and Pericardial Biopsy.

W. A. Hopkins, A. Alarcon, M. B. Davis and W. C. Wansker. Am. Surgeon 26:57-62 (Jan.) 1960 [Baltimore].

The authors report on 119 patients with pleural effusion, who were admitted to St. Joseph's Hospital in Atlanta, Ga., over a period of 19 months. Diagnosis was established in 90 patients (75%), while 29 left the hospital without an adequate diagnosis being established. The most common cause of pleural effusion is metastatic carcinoma, and such a diagnosis was established from the pleural fluid alone in 4 patients, and in 23 others by biopsy specimens obtained from the pleura, scalene node, or lung itself. Although complete history and physical examination, with adequate roentgenographic studies of the chest and study of the pleural fluid associated with bronchoscopy and scalene node biopsy, will establish the diagnosis in about 75% of the patients, needle biopsy should be employed at the initial thoracentesis in any patient with pleural effusion associated with a diagnostic problem. The authors performed an open biopsy on 23 patients with undiagnosed pleural effusion. Pulmonary tuberculosis was thus diagnosed in 5 patients, metastatic carcinoma in 4, pulmonary infarct in 2, lymphoma in 1, mesothelioma in 2, and chronic pleuritis in 9. Multiple biopsies of the pleura were obtained in all these patients. There were no empyemas, no deaths, and no serious complications associated with the biopsies. No case of pleural effusion should be allowed to go undiagnosed unless the condition of the patient does not warrant the necessary studan excision was done in only 10, but it is advisable to remove the cervical rib when symptoms attributable to neurovascular compression are present. Cervicodorsal sympathectomy with scalenotomy may be indicated in certain patients with arterial occlusion, thrombosis, or spasm. Careful preoperative evaluation, based on objective signs, rather than on subjective evidence, and repeated examination, may reduce the number of unsatisfactory postoperative results by eliminating some of the undesirable candidates for operation. Thorough exploration of the entire area of potential compression is necessary to assure acceptable results.

Follow-up Study of 500 Patients with Chronic Duodenal Ulcer Admitted to a Veterans Hospital. F. B. Thomson, E. P. McDougall and L. McIntyre. Surg. Gynec. & Obst. 110:51-54 (Jan.) 1960 [Chicago].

Five hundred patients with chronic duodenal ulcer were studied at the Shaughnessy Hospital in Vancouver, Canada. At the time of admission, clinical symptoms had been present in 95% of the patients for more than 2 years, in 85% for 5 years, and in 40% for 10 years. Vomiting was present in 222 patients, and was often an indication of impending intractability. Thirty-two per cent of the patients with this symptom required an operation at their first admission; and in a high percentage of those who were temporarily relieved by conservative medical treatment, other complications developed, raising the rate of surgical treatment to 68%. Intractable pain occurred in 214 patients, and in 79% of these it was associated with one or more complications. This symptom was the indication for 57% of all the patients who underwent definitive surgical treatment. Hemorrhage occurred in 31% of the patients. Only 32% of these did not respond to medical therapy. Perforation occurred in 47 patients (15%). Of these 47 patients, 62% required definitive surgery for intractable pain, pyloric obstruction, or hemorrhage within an average time of 17 months after the perforation. Duodenal obstruction, as indicated by gastric retention, was found in 17% of the patients and was the indication for 30% of all definitive operations.

The authors call attention to the fact that duodenal obstruction may exist in the absence of vomiting and of roentgenologic evidence. An hour of gastric aspiration during sleep should be a part of the routine examination of patients suffering from duodenal ulcer, and attention should be paid to any loss of weight, for it can be the result of a slowly increasing obstruction. Fifty-three per cent of all patients studied required surgical treatment; 43% of those who did not undergo surgical therapy continued to have symptoms. Of the 118 patients who suffered hemorrhage, 94% survived, 77% on medical treatment and 17% on combined medical-surgical treatment. This indicates that an episode of bleeding does not increase the likelihood that any particular ulcer will eventually require definitive surgical treatment.

Repair of Benign Strictures of the Bile Duct Involving Both or Single Hepatic Ducts. R. B. Cattell and J. W. Braasch. Surg. Gynec. & Obst. 110:55-60 (Jan.) 1960 [Chicago].

The authors report on the surgical treatment of 40 patients with biliary strictures, in whom either the bifurcation of the common hepatic duct had been destroyed or only one hepatic duct was involved. In 17 patients the repair was made in a 2-stage operation. In this type of surgical repair the anastomosis is constructed over a Y-shaped rubber tube, which is very useful in helping to shape the anastomosis during the time that it is in place. In the other operative procedures employed, the ducts were anastomosed to each other and to the lower end of the common duct in 4 patients; each hepatic duct was anastomosed separately to the jejunum in 5; the left hepatic duct was anastomosed to the jejunum in 3; dilatation of the right hepatic duct was performed in 9; and dilatation of both hepatic ducts and the common hepatic duct was performed in 3. Miscellaneous techniques, each one used only once in this series, were applied in 8 patients. Satisfactory results were obtained in 20 patients (60%), most of them surviving and being in good health for 3 years at the time of this study. There was an operative mortality of 3%; and 10% of the patients died after leaving the hospital, of complications of liver failure.

The procedure of choice for strictures in which the bifurcation of the common hepatic duct has been destroyed is anastomosis of the right and left hepatic ducts to each other, creation of a new common hepatic duct by division of the septum thus formed, and anastomosis of this new common hepatic duct either to the lower end of the common bile duct or to the jejunum. This anastomosis may be made over a T-tube or a Y-tube. The authors' present treatment of strictures involving only the right hepatic duct is dilatation through an incision made in the common hepatic duct and placement of a T-tube, one limb of which goes through the dilated portion of the duct.

GYNECOLOGY & OBSTETRICS

Hypertrichosis Associated with Ovarian Polycystosis: A Psychoendocrine Disease. R. E. Manfredi. Semana méd. 66:877-884 (Nov. 26) 1959 (In Spanish) [Buenos Aires].

Fifty patients with hypertrichosis and ovarian polycystosis were treated by 2 different methods: 25 patients received a medicosurgical therapy, and 25 received psychotherapy. The first signs of the hospital in the past 30 years among 237,714 admissions. The man complained of a "sense of uneasiness" in the left lower quadrant of his abdomen. This was associated with loose bowel movements and mild bloating. Gastrointestinal roentgenograms revealed a large posterior, apparently retroperitoneal mass displacing the greater curvature of the stomach anteriorly and cephalad, the jejunum to the right of the midline, and the colon inferiorly. The renal system on the left was elevated, distorted, and slightly compressed. The abdoman was opened through a midtransverse incision, and the tumor was found to be a large, relatively thin-walled cyst occupying the greater portion of the left half of the abdominal cavity. The cystic mass was fixed posteriorly by a broad vascular pedicle arising from the inferior mesenteric artery. A small vascular pedicle originated from the middle colic vessels and spread over the anterior aspect of the cyst. The cystic mass was removed intact, and the patient made an uneventful recovery. Examination of the surgical specimen revealed a unilocular celomic (mesothelial) cyst, originating in the transverse megacolon.

The woman was asymptomatic, and a slightly tender, freely movable, large round cystic tumor, easily palpable in the abdomen, was found on physical examination. A presumptive diagnosis of ovarian cyst was made. At laparotomy a large cystic mass was found in the mesentery of the jejunum. The cyst was dissected out except for a small portion of the wall which was so adherent to the mesenteric vessels that it was allowed to remain. Examination of the surgical specimen revealed a multilocular lymphatic or chylous cyst occurring in the mesentery proper (lymphangioma of the mesentery [cystic hygroma]). Postoperative course and convalescence were uneventful, and there has been no recurrence in the 10 years since surgical intervention.

Mesenteric cysts are rare and are of interest historically. Their causation, classification, and pathology have not been finally or clearly delineated, although they are almost certainly of congenital origin. The symptomatology of these cysts is related to their size and location in the abdomen, and they are frequently associated with some degree of intestinal compression or obstruction. Their treatment is surgical, and the mortality should be low. Review of the records of 4 hospitals in the vicinity of Los Angeles confirmed the incidence of true mesenteric cysts to be less than 1 per 100,000 admissions.

Inguinal Hernia in Pediatric Patients. C. W. McLaughlin Jr. and J. D. Coe. Am. J. Surg. 99:45-47 (Jan.) 1960 [New York].

It is now generally conceded that inguinal hernia the most common congenital lesion seen by the surgeon in infants and young children, should be repaired at once if the general condition of these small patients is satisfactory. The authors review their observations on 329 private surgical patients with inguinal hernia, in the pediatric age group, in whom 433 hernias were found. Ninety per cent (296 patients) were males, and 10% (33 patients) were females. In 53% of the children in this series the hernia made its appearance during the first year of life.

During the past 5 years the authors have explored the opposite side in the majority of routine herniorrhaphies for unilateral lesions in children under the age of 3 years. They do not follow this practice in premature infants, in the presence of incarceration, if the anesthetic is not well tolerated, or in the presence of other prohibiting complications. A 55% incidence of hernia on the opposite side was discovered, the figure being 49.3% if the initial hernia is right-sided and 69.6% if the primary hernia is on the left side. Incarceration was the most common complication observed in infants with hernia, 84% of these infants being under one year of age on admission. The surgical repair of inguinal hernia in infancy is a safe and practical procedure, and should be recommended as soon as the diagnosis is made.

Scalenus Anticus Symptoms: Evaluation and Surgical Treatment. D. H. Riddell, J. A. Kirtley Jr., J. L. Moore and R. S. Goduco. Surgery 47:115-124 (Jan.) 1960 [St. Louis].

The authors report on 21 men and 32 women, between the ages of 18 and 67 years, who underwent anterior scalenotomy for neurovascular compression symptoms of the upper extremities at the Vanderbilt University Hospital in Nashville, Tenn., during the past 15 years. Of these 53 patients, 34 (group 1) had evidence of scalenus anticus compression, without a cervical rib being present, and 12 (group 2) had similar symptoms, and a cervical rib, unilateral or bilateral, was found; in the remaining 7 patients (group 3) obstruction of the subclavian vein was the presenting symptom, which required both scalenotomy and incision of the subclavius muscle. The left upper extremity was involved in 31 patients, while the right upper extremity was symptomatic in only 15. Seven patients had evidence of bilateral neurovascular compression. Of the 46 patients in groups 1 and 2 who were presumed to have artery or nerve compression, 42 were followed up; 33 (80%) of these had obtained good results, 8 (18%) had fair results with continuing moderate symptoms, and 1 (2%) had a poor result. Of the 7 patients in group 3, 6 (80%) had obtained good results (relief of symptoms), and 1 had a fair result.

In the selection of patients for surgical treatment, it is desirable to have objective evidence of neurovascular compression rather than subjective symptoms alone. Of the 12 patients with a cervical rib, in twins is similar to that previously found in single deliveries; it is not changed in premature twins, or in twins delivered by a toxemic mother. The antibody titer in nonidentical twins is more variable than in identical twins. There is no significant relationship between the gamma globulin level and the antibody titer. The gamma globulin level in twins averages the same higher relative value as the maternal level in full-term deliveries; it is lower than the maternal level in premature twins or triplets. There is significant similarity between the proteic compounds of the twin's serum, either identical or nonidentical.

The lipidogram of the newborn infant is characterized by a high neutral fat and fatty acid content and a significantly low beta fraction and beta/alpha ratio. The alpha lipoprotein has almost the same absolute values in the mother as in the newborn infant. There is no significant difference between the lipidogram in twins, be they full-term or premature, identical or nonidentical. The cholesterol level in newborn infants is closely related to the lipidogram. There is a significant diminution of the cholesterol content of the beta lipoprotein in newborn infants, as compared with the maternal values. There is no uniform premeability for the examined constituents; no relationship has been found between the rate of transfer and the molecular size or molecular weight of the transferred constituents. In normal pregnancies, the placenta has apparently the same permeability throughout its entire area, as noted in identical and nonidentical twins. This was not found in a case of preeclamptic toxemia.

PEDIATRICS

Corticosteroids in Neonatal Jaundice. G. Murano and S. Auricchio. Ann. paediat. 193:342-352 (Dec.) 1959 (In English) [Basel, Switzerland].

The authors studied the effect of prednisolone and prednisone administered to 15 mature infants with neonatal jaundice of the physiological type and to 6 infants with the pathological type of hyperbilirubinemia of the neonatal period. Fifteen infants with neonatal jaundice received no treatment and were used as controls. The 15 children with physiological jaundice were given a daily dose of 10 mg. of hydrosoluble prednisolone intramuscularly for 10 days after birth. Results showed that the level of bilirubin in these children reached a maximum point on the 2nd day and dropped to a very low level on the 6th day, while the maximum point in the untreated group was reached between the 4th and the 6th day of observation. It was noted that in those infants who received constant treatment a sudden drop of the indirect fraction of bilirubin occurred, whereas a sudden increase in total bilirubin value, with an increase in the percentage of indirect reacting bilirubin and a reduction of the percentage of direct reacting bilirubin, occurred in a slightly jaundiced infant when treatment, consisting of one dose of 10 mg. of prednisone given orally on the 2nd, 3rd, and 4th days of life, was discontinued. Good results were also observed in an infant with severe jaundice caused by an accentuated hemolysis (not by isoimmunization) and with a completely indirect reacting hyperbilirubinemia, who was given one daily dose of 20 mg. of prednisolone intramuscularly. Therapy in this case caused an abrupt reduction of bilirubinemia (to 7.5 mg. per 100 cc.), not only with a reduction of hemolysis but also with a clear reduction of the percentage of indirect reacting bilirubin and an increase in the percentage of direct reacting bilirubin. Prednisone given orally to an infant with severe and early obstructive jaundice, high bilirubin level, and a moderate percentage of direct reacting bilirubin caused a drop in bilirubin values (to 20 mg. per 100 cc.), with a sudden reduction of indirect reacting bilirubin and a proportional increase in the percentage of direct reacting bilirubin. It is assumed that steroids act by reducing bilirubinogenesis, and they might also increase the capacity of the liver to conjugate bilirubin with glucuronic acid.

Studies on Acute Iron Poisoning. W. R. Bronson and T. R. C. Sisson. A. M. A. J. Dis. Child. 99:18-26 (Jan.) 1960 [Chicago].

The authors report experiments performed on 12 mongrel dogs. To avoid vomiting and to simulate the delay in treatment that might be expected in children with iron poisoning, solutions of ferrous sulfate were introduced directly into the jejunum of the dogs by syringe and needle after a midline exposure of the abdominal cavity. To determine the most effective mode of treatment with antidotes, such as disodium orthophosphate dihydrate in 20% solution, edathamil calcium-disodium in 2% solution, dog plasma, and dextrans of molecular weight of about 38,000 and 8,000, a variety of schedules were used. Two doses of ferrous sulfate in 25% solution were administered, giving 200 and 300 mg. per kilogram of elemental iron. Both of these doses were considered to be lethal and would have represented extreme danger to an infant ingesting such amounts. Three dogs served as contratest subjects; they were intoxicated with ferrous sulfate, but were not given any of the antidotes.

The administration of edathamil calcium-disodium did not prevent death, except in one animal which was also given disodium orthophosphate, but it lowered the serum iron concentration in dogs severely intoxicated by ferrous sulfate. The survival of dogs which received edathamil calcium-disodium alone or with the phosphate was prolonged beyond the time of death of the untreated contratest anisyndrome appeared in 1 patient before the age of 10 years; in 38 patients, between 10 and 20 years; in 9, between 20 and 30 years; and in 2, between 40 and 50 years. Adrenal gland specimens from total adrenalectomy performed on 2 patients showed moderate hyperplasia of the reticular zone. There were 3 main clinical pictures: (1) prevalence of hypertrichosis and luteinization, with heterosexual traits; (2) presence of ovarian cysts without tending to atresia, stratified granulosa, and scant reaction of stroma (possible hyperproduction of estrogens), with predominance of metrorrhagia and menorrhagia; and (3) dysplastic ovaries associated with hyporrhea and amenorrhea. Although the familial environment varied, in almost all the cases studied either the patient had been treated as a boy that the parents wished they had had, or there was preferential treatment granted to a brother. The urinary elimination of 17-ketosteroids was slightly above normal in 48 patients.

Twenty-five patients received prednisone and prednisolone in doses of 1 to 15 mg. daily during 8 to 16 months. In those with marked menstrual disturbances, the therapy was supplemented with wedge-shaped ovarian resection. The other 25 patients received deep psychotherapy (including hypnosis), followed or not by ovarian resection. At the end of one year of psychotherapy 100% of the patients in this group had become eumenorrheic; 96% had obtained either disappearance or a stationary stage of hypertrichosis, with 4% of recurrences; and 83.3% had had their fertility restored. These percentages were, in the medicosurgical therapy group, respectively, 80, 48, 52, and 33.3%. The author concludes that ovarian polycystosis associated with hypertrichosis is a psychoneuroendocrine condition involving a feeling of insecurity and a desire to be a man. This feeling causes, through the corticothalamohypothalamic axis, a disorganization of the basophil system in the anterior lobe of the hypophysis, which is responsible for the ovarian and adrenal alterations in this syndrome.

Association of Clinical Psychiatric Disease with Hyperemesis Gravidarum: A 3½ Year Follow-up Study of 48 Patients and 45 Controls. S. B. Guze, W. B. Delong, P. W. Majerus and E. Robins. New England J. Med. 261:1363-1368 (Dec. 31) 1959 [Boston].

Correlation between clinical psychiatric disease and hyperemesis gravidarum was investigated in a 3½-year follow-up study of 48 unselected hospitalized women with hyperemesis gravidarum and 45 unselected hospitalized women, used as controls, who had normal at-term delivery during 1954-1955. The follow-up study showed that 47 women (50%) were well, 20 had anxiety or hysteria, and 26 were probably ill. There was no significant statistical difference in the frequency of total psychiatric illness among the vomiters and the control group. Hysteria combined with probable hysteria was present in 7 vomiters (15%) and in only 1 control patient (2%). This suggests that there may be a relation between hysteria and some instances of hyperemesis gravidarum, but not between other psychiatric diseases and hyperemesis gravidarum. The results for the Negro patients were similar to those for the total series except that their differences for hysteria were not statistically significant.

Hyperemesis gravidarum was more common among ward than among private patients, the ratio being slightly more than 2 to 1. There was no indication that hyperemesis gravidarum was more prevalent in upper socioeconomic levels, as far as educational achievement or the occupational status of the husbands reflected such levels. The conclusion of this study is that hyperemesis gravidarum, on the whole, was not a manifestation of clinical psychiatric disease and that, in the few instances in which it appeared to be a manifestation of psychiatric illness, the only one involved was hysteria.

Studies in Placental Permeability: Transmission of Poliomyelitis Antibodies, Lipoproteins, and Cholesteral in Single and Twin Newborn Infants. M. M. Gelfand, G. J. Strean, V. Pavilanis and J. Sternberg. Am. J. Obst. & Gynec. 79:117-133 (Jan.) 1960 [St. Louis].

When the authors compared the electrophoretic pattern of parturient and cord blood, they established a significant increase in the relative level of fetal gamma globulin as compared with maternal gamma globulin. The problem of the placental transfer of poliomyelitis antibodies presented a special challenge, owing to the mass vaccinations. The authors hoped to time the vaccination of pregnant women so that the highest titer of maternal antibodies would coincide with the moment of maximum rate of transfer of the gamma globulins through the placenta. In further studies, answers to the following questions were sought: Is the placenta uniformly permeable for antibodies as well as for other constituents, as far as its entire area is concerned? In 2 separate placentas in one uterus (such as in the case of nonidentical twins), would it be possible to detect physiological or even pathological differences in permeability by examining the comparative rates of transfer of antibodies or even of other metabolites?

The maternal and the cord blood was taken from 2 groups of subjects: (1) 6 normal full-term single deliveries; (2) 7 deliveries of twins (4 identical, 3 nonidentical) and 1 delivery of triplets. In one mother, labor was induced at term because of preeclamptic toxemia; another set of twins was 10 weeks premature; and the set of triplets was of approximately 5½ months' gestation. It was found that the rate of transfer of poliomyelitis antibodies centration capacity. If vasopressin activity is lacking, hyposthenuria may result from the reduction of the osmolar concentration of the urine below that of the serum. In this way polyuria results from a water tolerance test (physiological diabetes insipidus), and in the presence of insufficiency of the neurohypophysis (hypophysial diabetes insipidus) polyuria results from reduced or incomplete formation of vasopressin. Reduced sensitivity of the kidney to an otherwise normal vasopressin level also can produce polyuria. This condition has been referred to as "nephrogenic diabetes insipidus," "water losing nephritis," or "water losing kidney."

Nephrogenic diabetes insipidus differs from the hypophysial form by the incomplete antidiuretic effect of vasopressin. The authors list a number of conditions, both congenital and acquired, which may be accompanied by nephrogenic diabetes insipidus, and present the histories of 2 patients with hyperthyroidism in whom they observed polyuria and an impairment of the concentration capacity. In one patient the polyuria persisted in spite of an elevated osmolar concentration of the serum. The administration of hypertonic sodium chloride solution exerted no antidiuretic effect. The second patient did not respond to vasopressin, which indicated that polyuria was due to nephrogenic diabetes insipidus. The excretion of ingested fluids was inadequate in both, but the disturbances disappeared after effective treatment of the hyperthyroidism. Temporary hypercalcemia was definitely present in the second and probably in the first patient. Twelve reports of hyperthyroidism combined with hypercalcemia were found in the literature; 9 of these patients had a history of polyuria or dehydration. In one of the 2 patients presented here, withdrawal of fluid resulted in extreme dehydration and the clinical symptoms of a thyrotoxic crisis. Thus, so-called thyrotoxic crises may possibly be caused by dehydration arising from nephrogenic diabetes insipidus.

Enhancing Effect of Corticotrophin Upon Exophthalmos Produced by Thyrotrophic Hormone.

J. Barraquer and J. M. Cañadell. Am. J. Ophth. 48:803-807 (Dec.) 1959 [Chicago].

In previous papers the authors presented clinical and experimental evidence to the effect that the exophthalmos characteristic of toxic diffuse goiter (Graves's disease) and the other related forms of ophthalmopathy (edematous exophthalmos, malignant exophthalmos, infiltrative ophthalmopathy, exophthalmic ophthalmoplegia) are secondary to a hyperfunction of the anterior pituitary. According to Aterman, the adrenal cortex also participates in the pathogenesis of these conditions. Experimenting with golden hamsters, the authors were able to confirm that the presence of the adrenal glands is indispensable to the provoking of exophthalmos by injections of thyrotropin and that previous treatment with corticotropin or adrenal steroids reinforces the exophthalmic action of the thyrotropic hormone. The experiments described in this paper were planned to study the effect of corticotropin on the exophthalmos produced in goldfish by intracelomic injections of thyrotropin and its influence on the eye protrusion obtained by injection of thyrotropin directly into the retrobulbar tissues.

It was found that goldfish respond to the administration of thyrotropic hormones with exophthalmos. Eye protrusion increases with simultaneous injections of corticotropin. Retrobulbar injections of isotonic sodium chloride solution, human serum, or pituitary hormones produce a transient exophthalmos, which is much more persistent when thyrotropin is injected. Previous treatment of fishes with long-acting corticotropin prolongs the duration of the exophthalmos caused by the retrobulbar injections of thyrotropin; this effect is not observed when other fluids are injected. The difficulties of producing exophthalmos in some fishes by the injection of anterior pituitary extracts or near pure thyrotropic preparations suggest the existence of an exophthalmic factor distinct from the thyrotropic hormone. The exophthalmos of toxic diffuse goiter and of related conditions probably develops by the effect of a combination of several endocrine factors. The action of thyrotropic hormone is the essential eliciting factor; the corticotropin and the activity of the adrenal cortex have a potentializing effect, possibly increasing the sensibility of the retrobulbar tissues to the exophthalmogenous action of thyrotropin.

Although the administration of thyroxin is known to exert an inhibiting effect on the pituitary secretion of thyrotropin, the authors observed in previous experiments that large doses of thyroid hormone increase the thyrotropic exophthalmos, while weak doses of the same are capable of reducing it. These results—apparently paradoxical—could be explained by the toxic action of thyroxin, which is capable of stimulating the anterior pituitary-adrenal system; it also increases the corticotropic and corticoid secretion and indirectly creates experimental conditions analogous to those obtained by injecting thyrotropin and corticotropin.

Hirsutism After Adrenalectomy.

J. A. Strong, J. Bruce and C. W. A. Falconer. Lancet 2:1055-1057 (Dec. 12) 1959 [London].

The authors present the histories of 2 spinsters, aged 60 and 57 years, respectively, who had severe hirsutism after being subjected to bilateral adrenalectomy and oophorectomy on account of metastatic cancer of the breast. They also present the case of a man, aged 73 years, with metastatic mammary carcinoma, in whom the beard continued to grow relatively vigorously after orchidectomy, adrenalectomy, and hypophysectomy. In 2 other women mals. Dog plasma did not combat shock and did not bind enough iron to prolong life. Neither dextrans with low molecular weight nor those with a weight of about 38,000 were effective in binding free iron in plasma through "protective colloid" action.

The widespread use of hematinics has increased the hazard of iron poisoning of infants and children. The symptoms are similar in humans and in dogs, thus making it possible to duplicate the events of accidental poisoning in the laboratory and to evaluate antidotal procedures. The use of edathamil calcium-disodium given intravenously and disodium orthophosphate given orally is suggested as an addition to the customary measures to combat shock, acidosis, and tissue damage in children with acute iron poisoning.

Duplications in the Gastrointestinal Tract in Children. E. R. Christensen. Danish M. Bull. 6:281-285 (Dec.) 1959 (In English) [Copenhagen].

Duplications in the alimentary tract are spherical or tubular structures, containing smooth musculature in the walls and lined with mucosa and intimately connected with a segment of the gastrointestinal tract. Duplications, as a rule, become apparent in early childhood but have been described at all ages. Six cases are reported in patients, aged from 2 days to 13 years, who were admitted to the pediatric department of the Rikshospital, Copenhagen, from 1950 to 1958. In 2 cases the site was the stomach; in 2, the small intestine; and in 1, the rectum; in 1 case there was duplication of both colon and rectum. Radical operation was performed in all cases, and follow-up showed that all the patients had normal alimentary function. In the infant with duplication of the rectum, a corrective cosmetic operation is still required. In differential diagnosis, Meckel's diverticulum, chylous cysts, and mesenteric cysts must be considered. A thorough roentgenologic examination is often of great diagnostic value. Treatment of duplication is always surgical, most often resection of the duplication and the attached segment of the intestine and primary end-to-end anastomosis. Every case of intestinal obstruction and hemorrhage from the gastrointestinal tract, even in the newborn infant, should suggest possible duplication. With timely pediatric surgery, with antibiotic cover and careful maintenance of the fluid balance, the prognosis is good.

Childhood Peptic Ulcer. A. Muggia and H. M. Spiro. Gastroenterology 37:715-724 (Dec.) 1959 [Baltimore].

This report is concerned with 24 children with peptic ulcer observed at the Yale-New Haven Medical Center. Five were less than one year old, the youngest being a prematurely born infant in whom massive bleeding and perforation were followed by death. The others ranged in age from 2 to 16 years. Three of the children had gastric ulcers; all others had duodenal ulcers. The clinical picture of peptic ulcer in children is often unlike that seen in adults. Bleeding, perforation, or a similar acute episode is usually the presenting manifestation up to the age of 2 years. After the age of 2, peptic ulcer is characterized by abdominal pain, increasingly typical as the child grows older.

Trauma has been suggested as the cause of the acute ulcer of the neonatal period. Such an acute ulcer may be associated with extensive body burns, with severe infection, or with cerebral disease. In children older than 2 years, chronic peptic ulcer seems to have the same basic "etiology" as in adults, including nervous and emotional factors and adverse environmental circumstances superimposed on a hereditary background.

Diagnosis depends upon awareness that peptic ulcer in children is atypical. Melena or hematemesis should suggest the possibility. The presence of hypersecretion in the stomach or indirect evidence of potential hypersecretion by elevated blood pepsin or uropepsin levels together with atypical symptoms may be enough to make the diagnosis. Response to therapy may be confirmatory. In the end, however, the diagnosis cannot be made on purely clinical grounds. Frequent repetition of gastrointestinal series with the hazards of exposure to radiation is inadvisable. Large ulcer niches are rarely demonstrated in children, so that the radiologist often must rely on pylorospasm and duodenal deformity for diagnosis. Irritability of the cap alone is too common in children to be a reliable sign.

A restricting diet has an unfavorable psychological effect on children, and a positive approach is to be preferred. They can be told to eat as frequently as they can, to drink extra milk between meals, and to avoid only the very obviously "bad" foods. Antispasmodics and antacids are rarely necessary in children. Evaluation of the family constellation is part of therapy. Response to such treatment has been good and prompt. Surgery should be reserved for the very seriously ill child.

ENDOCRINOLOGY

Nephrogenic Diabetes Insipidus in Hyperthyroidism. P. G. A. B. Wijdeveld, A. P. Jansen and C. L. H. Majoor. Nederl. tijdschr. geneesk. 103:2486-2492 (Dec. 5) 1959 (In Dutch) [Amsterdam].

The antidiuretic hormone of the neurohypophysis, generally designated as vasopressin, enables the kidney to increase by water retention the osmolar concentration of the urine in the tubule. There is evidence to suggest that the point of attack of vasopressin is located in the distal segment of the nephron and in the collecting system. Vasopressin insufficiency results in polyuria and reduced con-cryptococcosis, and sporotrichosis. The intraperitoneal administration of griseofulvin to white mice, experimentally infected with Candida albicans, did not result in the death of any of the animals, nor did it appear to enhance the severity of the infection. All tested species of nonpathogenic ascosporogenous and imperfect yeasts and yeast-like fungi were resistant to high concentrations of griseofulvin. Griseofulvin in high concentration did not affect the growth of a select group of pathogenic bacteria.

Griseofulvin had a very slight but consistent inhibitory effect upon the respiration of intact cells of T. rubrum, whereas the cytoplasmic energy centers were not affected at all. The addition of griseofulvin to normal serum appeared to result in a decline in the activity of the antibiotic, as determined by subsequent bioassay. The direct bioassay of body fluids was generally unsatisfactory, owing to the low levels of detectable antibiotic present in such materials and the presence of normal interfering substances. In the cultivation of skin scrapings from patients on griseofulvin therapy for evidence of biological cure, the antibiotic content of the skin does not appear to be a factor for concern, since direct inoculation of skin from such persons on appropriate mediums did not result in the inhibition of the resident fungus. An attempt to induce resistance to griseofulvin in T. rubrum by subculturing the organism in gradually increasing concentrations of the antibiotic over a prolonged period of time was not successful.

Melanotic Freckle: Lentigo Maligna. M. J. Costello, S. B. Fisher and C. P. DeFeo. A. M. A. Arch. Dermat. 80:753-771 (Dec.) 1959 [Chicago].

The authors report on the morphology, histopathology, therapy, and prognosis of melanotic freckle which is an easily recognizable pigmented precancerous macule frequently seen on the face of patients over 40 years of age. It usually exhibits a histopathological picture resembling a premalignant junction nevus, which can slowly progress to a tumor stage showing histopathological features of malignant melanoma. The histological appearance is dependent on the area and age of the portion of the lesion chosen for biopsy. Multiple subtotal biopsies of serial examination of the entire lesion will provide a more accurate interpretation. In the 10 cases described by the authors, the basic histopathological picture consistently seen was that of a junction nevus. However, features in certain areas suggest that it is a junction nevus of the premalignant type, and it is, therefore, difficult to differentiate these lesions histopathologically from early malignant melanomas. Individualized treatment, consisting of surgical excision or electrodesiccation and curettage, will provide good therapeutic, cosmetic, and functional results. Long-term observation of patients with this clinically distinctive lesion is necessary to corroborate the impression that the prognosis of a patient with a melanotic freckle is more favorable when compared with that of a patient with classic malignant melanoma.

INDUSTRIAL MEDICINE

Deafness Following Short-Term Exposure to Industrial Noise. S. L. Shapiro. Ann. Otol. Rhin. & Laryng. 68:1170-1184 (Dec.) 1959 [St. Louis].

The author calls attention to a type of deafness which has received little attention in the literature. He presents the histories of 6 patients in whom deafness resulted from a short-term exposure to industrial noise (usually for a few days). These patients had certain features in common. All were relatively young; 4 of the men were in their 30's, and none were over 43. None of them were steady workers with noisy equipment; as a rule, the particular job involved was performed in a small space with the noise close to one ear. The hearing of only this ear was damaged. As to the source of the noises, 2 involved sledge hammers; the rest came from pneumatic tools. The noise from the latter comes from both the tool and the object which it strikes, reaches a level as high as 125 db., and is a broad-band type of noise, ranging from 300 to 4,000 cps, with most of the frequencies in the highest or most objectionable portion of the spectrum. The results of the hearing tests in the 6 aforementioned patients indicated a high-grade perception deafness in one ear. The audiograms of these patients differed from those of 3 other men, in 2 of whom the hearing had been damaged after 15 years of exposure to industrial noise, whereas in the third man hearing had suffered little after 28 years' exposure to the noise of drop-forge hammers. Damage after chronic exposure tends to be bilateral, symmetrical, and partial.

The author feels that an unusual susceptibility to noise trauma must have existed in at least some of the men presented by him. He points out that the problem of the reduction of noise at its source is now being attacked by at least one manufacturer of pneumatic tools. Workers who have to use pneumatic and other noisy tools should be furnished with ear plugs and other protective devices.

Pulmonary Talcosis, a Clinical and Environmental Study. J. Messite, G. Reddin and M. Kleinfeld. A. M. A. Arch. Indust. Health 20:408-413 (Nov.) 1959 [Chicago].

In 1940, a chest x-ray survey of 221 talc miners and millers employed in several plants in St. Lawrence County, New York, disclosed pulmonary treated in the same way for mammary carcinoma, appreciable hirsutism was noted. Possibly the cortisone given as maintenance treatment was a sufficient source of androgenic steroid metabolites for hair growth to continue, but the amount of weak androgens likely to be formed in this way is small.

Hirsutism in the postmenopausal female after adrenalectomy and oophorectomy and beard growth in the male after orchidectomy, adrenalectomy, and hypophysectomy may have one or more explanations: 1. The excisions may have been incomplete, so that hormone secretion was not abolished. 2. Apart from the fraction converted to weak androgens, the cortisone given as replacement therapy after adrenalectomy may suffice to maintain abnormal hair growth or allow it to develop in the female, and may permit beard growth to continue in the male. Alternatively, hair growth of the type in question may not be "dependent" upon androgenic hormones for its continuance. If this is so, comparison is invited with the failure of many cancers of the breast to regress after adrenalectomy. The authors wonder why this phenomenon has not been reported more often, since they observed it in 4 of 61 patients treated for recurrent and metastatic mammary carcinoma by adrenalectomy and oophorectomy.

DERMATOLOGY

Effect of X-Rays on Sebaceous Glands of the Human Face: Radiation Therapy of Acne. J. S. Strauss and A. M. Kligman. *J. Invest. Dermat.* 33:347-356 (Dec.) 1959 [Baltimore].

The authors describe their studies in which the effect of roentgen irradiation on the human sebaceous glands was histologically investigated. Their studies were made on 23 male patients, between the ages of 15 and 30 years. All but 3 of the patients were inmates of a school for mental defectives. The irradiation was delivered at a target-skin-distance of 20 cm. from a Picker Portable Superficial Therapy Unit. The half-value of the radiation was 0.85 mm. of aluminum. Fractional therapy was given through an open port, centering the target over the zygomatic process with appropriate shielding of the surrounding areas. Single doses were administered through a cone, 2 cm. in diameter. All the patients had acne, except a few receiving single doses. No other kind of treatment was given. Control biopsy specimens of the contralateral cheek were obtained before treatment. Biopsy specimens of treated areas were removed at different intervals. The specimens were sectioned serially and stained with hematoxylin and eosin.

The following single-dose treatments were given: Three patients were given 300 r; 4 patients were given 400 r to one cheek and 800 r to the opposite cheek; and 2 patients were given 1,500 r to an area of the cheek, 2 cm. in diameter. Fractional doses of 75 r or 150 r were given at weekly intervals up to a total of 900 r or 1,200 r. The authors found that, while the large sebaceous glands of the human cheek are relatively radiosensitive, being moderately suppressed by a dose of 400 r, these glands have a tremendous potential for regeneration. After the administration of 1,200 r in fractional dosages, recovery is complete in 4 months. Even after a single dose of 1,500 r, there is considerable sebaceous regeneration at one year. The effect of x-ray therapy on the acne process is mediated through sebaceous gland suppression; it is not anti-inflammatory. The most satisfactory results are obtained with prolonged fractional therapy of 75 r per week, thereby suppressing the glands for a longer period. The clinical remission is usually temporary; acne recurs when the glands regenerate.

In Vitro Studies of the Antifungal Antibiotic Griseofulvin. F. J. Roth Jr., B. Sallman and H. Blank. *J. Invest. Dermat.* 33:403-418 (Dec.) 1959 [*Baltimore*].

The antibiotic, griseofulvin, was first isolated from Penicillium griseofulvin in 1939. The therapeutic efficacy of orally administered griseofulvin for the treatment of superficial fungous infections due to dermatophytes seems established. The authors reported in 1959 that griseofulvin, administered by mouth in daily doses of 1 Gm., proved to be a highly effective antibiotic for the treatment of 31 patients with dermatomycoses. In this paper they describe observations on the effect of griseofulvin on the in vitro growth of (1) dermatophytes and (2) other mycotic agents, pathogenic bacteria, and saprophytic fungi and yeasts; also, (3) on the effect of griseofulvin on the respiration of Trichophyton rubrum and (4) on the bioassay of griseofulvin in body fluids and tissues.

Thirteen species of dermatophytes were assayed for sensitivity to griseofulvin by use of both the tube and the plate assay methods. A high degree of in vitro sensitivity was demonstrated in all 13 species. Low concentrations of the antibiotic inhibited their growth and produced bizarre abnormalities in their hyphal structure. Higher levels of the antibiotic resulted in an apparent complete arrest of the growth of the mycelium. The action of griseofulvin on dermatophytes appears to be limited to fungistasis. These fungi were able to withstand prolonged exposure to high concentrations of the antibiotic without loss of viability. Griseofulvin failed to demonstrate significant in vitro inhibitory activity against the etiological agents of histoplasmosis, North American and South American blastomycosis, candidiasis, chromoblastomycosis, nocardiosis, geotrichosis, aspergillosis, Results from both trials showed that the groups receiving antibiotics were greatly benefited, as compared with the groups receiving placebo capsules. Improvement was judged on the basis of reduction in the number and severity of acute exacerbations. by eradication of Hemophilus influenzae and Diplococcus pneumoniae from the sputum, and by statistical comparison of sickness in the treated as against the untreated groups. A significant rise in antibody titer to the influenza viruses was demonstrated in 14 patients during the second trial, but only 3 of them had clinical influenza. Subclinical infection in the remaining 11 patients did not obviously affect their bronchitis. Side-effects were infrequent and not serious. Diarrhea was mildly troublesome in 15 out of 47 patients receiving antibiotics. Gross disturbance of normal surface flora of the respiratory and intestinal tracts was not evident. Antibiotic-resistant strains of coliform species and Staphylococcus aureus occurred in some patients, mainly in those receiving antibiotics, but they were not significantly associated with clinical deterioration. It was found practicable to manage the patients on an outpatient or domiciliary basis. This had the advantage of a lower over-all cost than hospital treatment, which, in any case, carries with it the attendant dangers of superinfection with antibiotic-resistant, and often highly virulent, microorganisms. It is concluded that continuous daily oxytetracycline therapy in advanced cases of chronic bronchitis, though apparently expensive, is less costly than the treatment of exacerbation of the disease in hospital.

Prevention of Venous Thrombosis and Pulmonary Embolism in Injured Patients: A Trial of Anticoagulant Prophylaxis with Phenindione in Middle-aged and Elderly Patients with Fractured Necks of Femur. S. Sevitt and N. G. Gallagher. Lancet 2:981-989 (Dec. 5) 1959 [London].

The authors report on 300 patients, between the ages of 55 and 85 years, with fractured hips, admitted to the Accident Hospital, in Birmingham, England; 150 of these patients were given phenindione to prevent venous thrombosis and pulmonary embolism, while 150 others did not receive the prophylactic treatment with phenindione. The 2 groups of patients were otherwise comparable. Phenindione therapy was begun soon after admission to the hospital, usually with an initial dose of 200 mg. of the drug, followed the next day by 100 mg. and then 25, 50, or 75 mg. daily. Small doses of 25 mg. often sufficed in the few postoperative days, while larger doses of 50 to 100 mg. were necessary in convalescence. Therapy was generally continued until satisfactory mobility was restored. Treatment was controlled by repeated estimations of the plasma prothrombin time, which was prolonged to between 2 and 3 times the normal. Such prophylaxis was found practicable and safe, and the fractures were pinned or nailed without significant hemorrhage.

Embolism occurred in none of the patients under the current influence of phenindione; but in the control group embolism occurred in 18%, and fatal embolism in 10%. Two cases of fatal embolism and one of minor embolism occurred among the patients who had received phenindione, but only after therapy had been discontinued. Clinical venous thrombosis occurred in 28.7% of the control group, compared with 2.7% of the group undergoing phenindione therapy. Significant or extensive thrombosis was observed at autopsy in 29 (83%) of 35 patients in the control group, compared with that in 3 (14%) of 21 patients who had received phenindione therapy; these 3 patients had died after discontinuation of phenindione therapy. In most of the patients treated with phenindione, the whole lower venous tree was completely free of thrombi. These findings indicate that phenindione effectively prevents thrombosis in veins and eliminates the risk of pulmonary embolism in patients under its influence, provided that the drug is given early, for sufficient time, and under laboratory control.

Long-Term Results in Treatment of Diabetes Mellitus with the Sulphonylureas. C. K. Gorman and J. A. Weaver. Brit. M. J. 2:1214-1217 (Dec. 5) 1959 [London].

The authors studied the results of treatment with tolbutamide administered orally to 291 diabetic patients treated for periods of up to 2½ years. Sixty of the 291 patients had previously received treatment with insulin, whereas the remaining 231 patients had not been given treatment with insulin, but they had been attending the clinic for periods of a few months to 20 years, and an attempt to control the diabetes by a reduction of the amount of carbohydrate in the diet had been made in them. Treatment with tolbutamide was started when it had been discovered that the hyperglycemia and glycosuria were increasing despite adherence to the diet. Treatment with tolbutamide was successful in 187 of the 231 patients not previously treated with insulin, while it was a therapeutic failure in the remaining 44. Of the 187 patients treated successfully, 46 were men, with an average age of 63 years, and 141 were women, with an average age of 65. The average duration of the diabetic condition among the men was 1 year and 8 months, and that among the women was 3 years and 6 months. The average weight of the men was 154 lb. (69.9 kg.), and that of the women was 139 lb. (63 kg.). The average fasting blood sugar level among the men was 199 mg. per 100 cc. before treatment and 107 mg. per 100 cc. after treatment; it was 233 mg. per 100 cc. before treatment fibrosis in 32 workers, 18 of whom had had no other occupational dust exposures. This survey clearly indicated that exposure in these talc mines and mills was capable of producing a fibrogenic type of pneumoconiosis. As a result, a more effective medical and engineering program was recommended, and this was instituted between 1943 and 1948. In 1954, a follow-up study of the 32 workers with pulmonary fibrosis disclosed that the pneumoconiosis was progressive and disabling, but that the progression was slow and the disability involved primarily an older age group than that seen in silicosis. An environmental evaluation performed at the time, as indicated by dust counts at various operations in these mines and mills, revealed a marked improvement in the engineering control. The studies presented here were planned in 1954 and carried out in 1958. They were concerned (1) with follow-up studies of the talc miners and millers in St. Lawrence County, (2) with the comparison of the medical and environmental data in the talc mines and mills in 2 different regions of the state, and (3) with the significant differences observed in these studies.

The authors found that, although the incidence of pulmonary talcosis in the millers has not changed appreciably, the severity and the progression of the disease have been diminished. The reduction in the dust exposure in the mines and the lower incidence of pulmonary fibrosis among the talc miners are primarily due to the institution of wet drilling. A comparative study of talc millers in 2 different regions of New York State showed that, while the degree of exposure to talc dust was similar, the incidence and severity of the talc pneumoconiosis were considerably less where the exposure was to the nonfibrous variety of talc. The data indicate that, while both types of talc can roduce pulmonary fibrosis, the fibrous, or tremo- ie, variety is the more pathogenic.

Pollution Hazards from Diesel Locomotive raffic in a Railway Tunnel. M. Katz, R. P. Rennie d Z. Jegier. A. M. A. Arch. Indust. Health 20:493-04 (Dec.) 1959 [Chicago].

A study was made of the extent of air contamination from the exhaust gas of 1,750-h.p. diesel locomotives while hauling freight and passenger trains through the St. Clair Tunnel, linking Sarnia, Ont., with Port Huron, Mich. The tunnel railway system was under electrified operation, but plans for the dieselization of this section of the line raised the problem of the extent of air pollution to be anticipated from diesel exhaust fumes in the tunnel. The purpose of this survey was to determine the concentration levels of smoke, particulate matter, and principal gaseous contaminants from diesel trains operated in accordance with the normal freight and passenger traffic schedules; to determine the rate and pattern of air flow through the tunnel induced by the train movement; to assess the possible health hazards due to the tunnel atmosphere; and to evaluate the ventilation requirements for safe environment conditions. Atmospheric sampling tests were conducted. In all, more than 2,000 observations were made. The St. Clair Tunnel has a length of 6,032 ft. and, at its midpoint, lies 25 ft. beneath the bed of the St. Clair River. At the time this study was being carried out, the tunnel was without forced ventilation.

The mean concentrations of toxic gases in the St. Clair Tunnel during the 3-day period of these trials, when all train movement was dieselized, were, in general, below the threshold limits established by the American Conference of Governmental Industrial Hygienists. There were no abnormal health effects observed on participants during 8-hour exposures to the tunnel atmosphere, with the exception of some minor cases of eye-and-throat irritation on 3 brief occasions. Nevertheless, in view of the levels of oxides of nitrogen, aldehyde, smoke, and particulate matter attained under conditions of maximum contamination, adequate forced ventilation of this tunnel has been recommended, to be installed before full dieselization is introduced to replace electrical operation of trains.

THERAPEUTICS

An Evaluation of Continuous Antibiotic Therapy in Chronic Bronchitis. J. McC. Murdoch, W. J. Leckie, J. Downie and others. Brit. M. J. 2:1277-1285 (Dec. 12) 1959 [London].

The authors report the clinical and bacteriological results of 2 double-blind trials of continuous tetracycline and oxytetracycline therapy carried out during the periods 1957-1958 and 1958-1959 at the Royal Infirmary in Edinburgh. During the earlier period 23 patients were observed, and in the later period 75 patients, including 20 from the previous winter. Each patient had had chronic bronchitis for 5 years or more, characterized by a persistent cough, exertional dyspnea, and recurrent winter invalidism due to acute exacerbations of the disease. Of the 23 patients, 12 received one capsule 4 times daily, containing Signemycin (167 mg. of tetracycline and 83 mg. of oleandomycin phosphate), and the remaining 11 patients received inactive capsules, containing lactose. Of the 75 patients, 35 received one capsule 4 times daily, containing 250 mg. of oxytetracycline alone as the active agent, and the remaining 40 patients received inactive capsules, containing lactose. During both winters the assessment of each patient was based on the subjective and objective findings entered at each interview every 2 weeks.

claudication is useless. Vasodilators usually decrease blood flow in an extremity which has been subjected to sympathectomy, and, therefore, these drugs should not be used in an attempt to augment the effect of sympathectomy. Finally, the response to a vasodilator drug gives no indication of the response to sympathectomy. Such a preoperative test is without value and may lead to a suitable patient being refused sympathectomy. Much unnecessary prescribing and expense would be saved, if these observations were recognized.

The Effect of Insulin-binding Serum Globulin on Insulin Requirement. T. E. Prout and R. B. Katims. Diabetes 8:425-431 (Nov.-Dec.) 1959 [New York].

Previous investigations by other workers revealed the presence of an insulin-binding globulin in the serums of patients with diabetes mellitus treated previously with insulin. In an attempt to determine the effect of this insulin-binding globulin on the insulin requirements of patients with diabetes mellitus, the authors administered intravenously insulin labeled with radioiodine (insulin I^{131}) to 3 men and 3 women, between the ages of 34 and 74 years, with diabetes mellitus, and to one 50-year-old man with hypoglycemia resulting from a previous gastric operation. The doses of the radio-insulin administered varied from 0.3 to 3.6 units of insulin and from 75 to 150 μc of I^{131}. Propylthiouracil in doses of 100 mg. and potassium iodide in doses of 0.5 Gm. were given to each of these patients every 8 hours for 2 days before and for 5 days after the injection of radioinsulin, to prevent thyroidal accumulation of iodine and to promote excretion of the degradation products of the radioinsulin. Venous blood samples were obtained from these patients at various intervals after the intravenous administration of radioinsulin, and the intact insulin contained in each serum was separated by electrophoresis.

The results showed that the insulin-binding globulin in the serums of these patients had an effect on their insulin requirements. The amount of insulin that is available for peripheral use is inversely proportional to the quantity of unsaturated binding protein of the serum. Some injected insulin was found in the unbound form, however, despite high levels of insulin-binding globulin, presumably by dissociation from the insulin bound to globulin. Increasing the daily dosage of insulin saturates the binding globulin and allows a greater proportion of the injected insulin to remain in the unbound or free form. The increased insulin dosage may stimulate further production of the insulin-binding globulin. Administration of methylprednisolone decreased the total binding capacity of the serum in one patient tested. Thus, the degree of saturation of the binding globulin as a result of previous insulin therapy, the degree of dissociation between the bound and the unbound insulin, and the rate of production of insulin-binding globulin in addition to the total insulin-binding capacity of the serum appear to influence insulin requirements in patients with diabetes mellitus previously treated with insulin.

North American Blastomycosis. E. R. Harrell and A. C. Curtis. Am. J. Med. 27:750-766 (Nov.) 1959 [New York].

The results of the intravenous administration of amphotericin B to 8 men, between the ages of 24 and 69, with North American blastomycosis of various duration, are reported. Pulmonary, cutaneous, and osseous involvement of varying degrees of severity was observed in all 8 patients. In 5 patients, who had negative blastomycin skin tests, the disease presented in a most severe form; 4 of them had positive complement-fixation tests. All 5 had been treated with aromatic diamidines without achieving any improvement. Amphotericin B was administered in daily doses of 50 to 100 mg., suspended in 1,000 cc. of 5% dextrose in water, by slow intravenous drip over a period of 6 to 8 hours. The total dose was 1 Gm. for 5 patients and 1.5 Gm. for 1, while the remaining 2 patients received 4 and 4.5 Gm. respectively.

Six patients obtained an apparent clinical cure, while in 2 the recovery was neither complete nor permanent. The latter required repetition of the therapy in order to control the disease. Although the optimal total dose necessary for complete recovery was not established in this study, it seems that North American blastomycosis requires a smaller dosage of amphotericin than cryptococcosis, histoplasmosis, or coccidioidomycosis. Seven of the eight patients developed symptoms of toxicity during the administration of amphotericin B. Azotemia and urinary casts were the most serious toxic reactions, but they subsided with the interruption of the therapy for a few days. Fever, nausea, emesis, and malaise were minimized by the simultaneous administration of corticosteroids with amphotericin. The authors advise that the drug should be given every other day, instead of daily, in order to lessen the toxic effects.

Carcinoma of the Breast Treated with Thio-TEPA. H. Holden and B. Sundstrup. M. J. Australia 2:671-675 (Nov. 7) 1959 [Sydney].

The cases of 5 women, 33 to 71 years of age, with advanced carcinoma of the breast who were treated with triethylene thiophosphoramide (thio-TEPA) are presented. One patient received 147 mg. of the drug intravenously over a period of 11 days, and another received 90 mg. intravenously over 10 days; of the remaining 3 patients, one received and 123 mg. per 100 cc. after treatment among the women. The average fasting blood sugar level at the end of the observation period was 103 mg. per 100 cc. among the men and 117 mg. per 100 cc. among the women. Of the 44 patients in whom treatment with tolbutamide was a failure, 20 were men, with an average age of 56 years, and 24 were women, with an average age of 24 years. The average duration of the diabetic condition among the men as well as among the women was 3½ years. The average fasting blood sugar level was 294 mg. per 100 cc. before treatment among the men and 276 mg. per 100 cc. among the women, while it was 243 mg. per 100 cc. after treatment among the men and 225 mg. per 100 cc. among the women. The proportion of initial failures to treatment was 15% in the female group and 30% in the male.

The 60 patients who had received treatment with insulin were successfully transferred to treatment with tolbutamide. Their average age was 68 years, and the average previous dose of insulin was 22 units daily. Tolbutamide was given after meals 2, 3, or 4 times daily. Thirty-two of the 187 patients in whom treatment with tolbutamide was successful were given a total daily dose of 1 Gm.; 41 patients, 1.5 Gm.; 75 patients, 2 Gm.; and 39 patients, 3 Gm. The toxic effects observed were few. Findings with regard to the type of patient suitable for treatment with tolbutamide show that selection can be made by the response to a single oral dose of the compound. A fall of 30% in the blood sugar from the fasting level at 3 or 4 hours is regarded as indicating suitability for long-term treatment. Studies on the assimilation of dextrose administered intravenously indicated that the ability to utilize carbohydrate had not been adversely influenced by prolonged treatment with tolbutamide.

Thyrotoxicosis Treated with Small Repeated Doses of Radioiodine. E. L. De Gowin, R. E. Hodges, H. E. Hamilton and T. C. Evans. A. M. A. Arch. Int. Med. **104**:959-965 (Dec.) 1959 [Chicago].

The authors report on 338 patients with thyrotoxicosis, who were treated with radioiodine (I^{131}) at the thyroid clinic of the University Hospitals in Iowa City. The greatest number of patients were between the ages of 30 and 39 years, but nearly as many were in each of the 2 following decades, and 21 patients were over 70 years of age. Of the 338 patients, 199 (58%) were classified as having diffuse goiters, 62 (18%) had nodular goiters, 53 (15%) had goiters recurring after thyroidectomy, and in 24 (7%) examiners disagreed on the type of gland or could palpate no thyroid tissue. In these patients, the arithmetic mean of the single administered doses of I^{131} was 4.6 mc. The patients were observed at 3-month intervals for at least 6 months after the euthyroid state had been attained or until permanent myxedema from therapy had been shown. Control of the disease was achieved in 60% of the patients with a single dose of I^{131} and in 86% with one or two doses. The over-all incidence of permanent myxedema was 9.1%. In one patient thyroid storm occurred during treatment. No instances of irradiation thyroiditis were observed. These results compare favorably with those obtained by other workers in other series of patients treated with higher average doses of I^{131}. The authors prefer to subject their patients to less irradiation with an average dose of 4.6 mc. of I^{131} and achieve control of 86% of the patients with one or two doses, rather than increase the average dose and control more patients with one dose, thereby subjecting them to irradiation thyroiditis and thyroid storm.

The Case Against Vasodilator Drugs in Occlusive Vascular Disease of the Legs. J. A. Gillespie. Lancet **2**:995-997 (Dec. 5) 1959 [London].

The author studied the effect of 4 vasodilator drugs, namely, tolazoline (Priscoline) hydrochloride, phenoxybenzamine hydrochloride (Dibenzyline), chlorpromazine (Largactil), and promazine, on the blood flow in the feet and calves of patients with ischemic skin lesions or rest-pain of the feet, of patients with intermittent claudication, and of patients who had undergone sympathectomy for occlusive arterial disease. Blood flow in the feet and calves of these patients was measured by venous-occlusion plethysmography, with use of water-filled plethysmographs at constant temperature in a constant-temperature laboratory. The blood flow was measured at half-minute intervals. The resting flow was the mean of 20 consecutive measurements, and the postvasodilator blood flow was calculated similarly 15 minutes after intravenous injection of the drug. To relieve rest-pain or ischemic skin lesions, the vasodilator drugs must increase blood flow in the foot. To relieve claudication, they must increase muscle blood flow in the calf. The measured change in the blood flow which these drugs produce will at once indicate their usefulness; if they do not increase blood flow, they cannot have any therapeutic value.

The results of this quantitative study on the effect of the vasodilator drugs on the blood flow have shown that vasodilator drugs are not likely to increase blood flow in the ischemic foot, and the fall in blood flow which often follows their administration could prove disastrous to the critically nourished foot after an acute occlusion. Whether given by mouth or intravenously, these drugs have no place in the treatment of acute arterial occlusion, or of the chronically ischemic foot. As vasodilators do not increase muscle blood flow in the calf, and often decrease it, prescribing them for intermittent mellitus than in the metabolically normal men. Mean fasting plasma insulin activity was 59 microunits of effective insulin concentration per cubic centimeter of plasma in normal men; 103 microunits per cubic centimeter in tolbutamide-responsive adults with diabetes mellitus; 36 microunits per cubic centimeter in tolbutamide-nonresponsive adults with diabetes mellitus; and 1 microunit per cubic centimeter in juvenile patients with diabetes mellitus. One hour after the ingestion of 100 Gm. of glucose, respective values were 573 microunits per cubic centimeter in normal men; 453 microunits per cubic centimeter in tolbutamide responders; 77 microunits per cubic centimeter in tolbutamide nonresponders; and 3 microunits in the juvenile patients.

Compared with an insulogenic index of 100% for normal men, corresponding indexes were 25% for tolbutamide responders, 4% for tolbutamide-nonresponsive patients, and 0.1% for juvenile patients with diabetes mellitus. These data indicate that total insulogenic reserve is sharply reduced in patients with diabetes mellitus, even when apparent impairment of carbohydrate tolerance is minimal; that the insulogenic reserve drops progressively as the patients' clinical condition worsens; and that it approaches zero in the "total diabetic." It thus was found that patients with diabetes mellitus of increasing severity revealed diminishing insulogenic reserve, not only by progressive lower titers of fasting plasma insulin activity but also by proportionately smaller increments of circulating insulin activity in response to a glycemic stimulus.

Comparison of the Treatment of Hypercholesteremia with Nicotinic Acid, Sitosterol, and Safflower Oil. K. G. Berge, R. W. P. Achor, N. W. Barker and M. H. Power. Am. Heart J. 58:849-853 (Dec.) 1959 [St. Louis].

The association of hypercholesteremia and atherosclerosis has stimulated attempts to reduce elevated levels of cholesterol in the blood by various means. In 1955, Altschul and associates observed that large oral doses of nicotinic acid decreased concentration of cholesterol in the serum of human beings. A number of investigators, including the authors, were able to confirm the effectiveness of orally administered nicotinic acid in patients as well as in experiments on animals (rabbits fed with cholesterol). The authors used large doses of nicotinic acid (Niacin) in the treatment of 54 patients with hypercholesteremia, and these were followed for from 3 months to 3 years. The investigations were undertaken to assess the use of Niacin in the treatment of hypercholesteremia by comparing its effectiveness with that of 2 other agents in current use, namely, safflower oil and sitosterol. Ten patients with hypercholesteremia who had received large doses of Niacin for intervals of 9 to 17 months, and who had received a placebo for 3 months, were selected for study. The daily dose of Niacin ranged from 4.5 to 6 Gm., and averaged 5.3 Gm., during the 3 months or longer that each patient received his maximal dosage, which was given in divided doses with each meal. The effects of safflower oil and sitosterol were also studied for 3 months each. The diet of the patients was not restricted with regard to the amount or type of fat.

It was found that the oral administration of large doses of Niacin was more effective in lowering plasma cholesterol than was either safflower oil or sitosterol. The simultaneous administration of Niacin and sitosterol was more effective than the use of either agent alone, and their combined effects were nearly additive. As compared with safflower oil or sitosterol in the treatment of hypercholesteremia, Niacin has several practical advantages in that the drug is inexpensive, is simple to administer, and does not require alterations in the patient's dietary habits. However, the safety of such long-term use of Niacin must be established before this form of therapy can be regarded as other than an investigational procedure.

Acute Meprobamate Intoxication: Seven Cases with Coma as Dominating Symptom. H. Hals. Nord. med. 62:1578-1581 (Oct. 29) 1959 (In Norwegian) [Stockholm].

During the past 2½ years 7 cases of acute meprobamate poisoning, in 4 men and 3 women, previously well, were treated in Haukeland Hospital in Bergen, Norway. These patients were all discharged without demonstrable sequelae. Three of them had taken the drug in attempted suicide; the others, apparently to produce a pleasant carefree state. The main symptom in all the cases was coma lasting from 10 to 36 hours, with decreased tone of skeletal muscles and loss of tendon reflexes. In 2 cases arterenol had to be given because of grave hypotonia. Treatment for acute meprobamate intoxication follows the same lines as for every other condition with coma as the main symptoms. It is important to bear in mind that meprobamate has a marked euphorizing effect, which can lead patients to ingest large doses. Simultaneous ingestion of alcohol predisposes to the development of coma and hypotension.

Guanethidine: Hypotensive Drug with Prolonged Action. A. W. D. Leishman, H. L. Matthews and A. J. Smith. Lancet 2:1044-1048 (Dec. 12) 1959 [London].

The authors first review earlier experimental and clinical studies on the hypotensive drug, guanethidine, including the report by Page and Dustan in The Journal (170:1265-1271 [July 11] 1959). Their own observations are based on the oral administration of guanethidine to 25 hypertensive patients (10

85 mg. and the other 2 received 80 mg. intramuscularly over a period of 5 days. Treatment with thio-TEPA was repeated in all the patients with the exception of one who died. All of them showed remarkable relief of pain within 4 days of commencing thio-TEPA therapy. The first 2 patients had relapsed into pain after control with fluoxymesterone for 6 months, so that there is no doubt that in these patients relief of pain was due to thio-TEPA. All the patients were so relieved that the heavy sedation previously necessary was reduced to an occasional oral dose of a mixture containing morphia and aspirin. Three of the 5 patients were able to walk again and returned home. The character of the bone metastases altered little in all the women and was extensive.

The authors point out that, despite the fact that thio-TEPA is very toxic to the leukoerythropoietic tissues, the dramatic improvement in the general condition of the patients treated makes further trial by this agent necessary. Regression of soft-tissue primary and secondary metastases occurred in 2 patients; another patient developed pulmonary secondary metastasis while waiting for the return of a normal blood picture before another course of treatment was started. Involvement of the liver by metastases appears to be a special problem, possibly because of the deamination function of this organ. In order to increase the dosage of thio-TEPA and to increase its effect, some satisfactory method of protecting the bone marrow elements, in addition to that afforded by androgen, is necessary. The authors believe that the bone marrow depression in the 5 patients presented may have been due to the considerable amount of marrow replaced by malignant infiltration. Vitamins B_1, B_2, B_6, B_{12}, nicotinic acid, leucovorin (folinic acid), and all essential enzymes in tissue oxygen exchange, and presumably cellular metabolism also, as well as an adequate supply of the vitamins known to be essential to leukoerythropoiesis, may be a selective method of protecting the marrow and retaining the effects of thio-TEPA.

Three Fatal Anaphylactic Reactions Caused by Penicillin. A. F. Schiff and J. H. Davis. J. Florida M. A. 46:707-708 (Dec.) 1959 [Jacksonville].

The first of the 3 cases of fatal anaphylactic reaction presented was that of a 30-year-old woman, who in the emergency department of a hospital, on the basis of a diagnosis of pelvic inflammatory disease, was given an intramuscular injection of 2.4 million units of procaine penicillin G. A few minutes later she became pale, faint, and lost consciousness. Neither pulse nor blood pressure could be obtained. The patient was pronounced dead a little over an hour from the time she was first given the penicillin injection. Most of this hour was used in efforts to revive her. An autopsy showed only minimal pulmonary emphysema consistent with anaphylaxis and slight cerebral edema. In case 2, a 65-year-old woman, because of a cold that had lingered on for 10 days, was given 450,000 units of procaine penicillin G into the gluteal muscle. Within 2 or 3 minutes she started foaming at the mouth, became faint, pale, and died. In case 3, a 21-year-old woman, 8 weeks pregnant, was seen in a hospital emergency room with complaints of pains in the lower right quadrant of the abdomen and slight vaginal bleeding. She was given an intramuscular injection of 600,000 units of procaine penicillin G. She was pronounced dead approximately 25 minutes after the penicillin injection.

Despite numerous warnings against the injudicious use of penicillin, deaths continue to occur under circumstances in which a more prudent calculation of the risks involved should have been considered. These deaths unfortunately appear to be on the increase. They have been well documented in the medical literature. The true incidence, however, is unknown, since the fear of medicolegal consequences prevents all cases from being reported as such. Nevertheless, the fact that these deaths are occurring in greater frequency cannot be denied. This increase is due to the fact that penicillin is the most allergenic of all antibiotics, that an increasing portion of the population is becoming sensitized because of repeated exposure to penicillin, and that, because of its cheapness, penicillin is the most extensively used antibiotic in America.

Plasma Insulin Activity After Glucose: An Index of Insulogenic Reserve in Normal and Diabetic Man. H. S. Seltzer and W. L. Smith. Diabetes 8:417-424 (Nov.-Dec.) 1959 [New York].

The authors determined the plasma insulin activity during fasting and one hour after ingestion of 100 Gm. of glucose in 12 metabolically normal men, 9 elderly men with diabetes mellitus whose fasting blood sugar level was moderately elevated and subsequently was easily controlled by diet alone or combined diet and daily administration of tolbutamide (tolbutamide responders), 6 other elderly men with diabetes mellitus who did not respond to combined diet and tolbutamide therapy (tolbutamide nonresponders), and 5 juvenile male patients with diabetic mellitus in whom severe ketonuria promptly developed when exogenous insulin was reduced. Only 2 patients were obese. An "insulogenic index," relating enhancement of circulating insulin activity to magnitude of glycemic stimulus, enabled comparison of the insulin-secreting capacity of the 4 groups.

Average fasting blood glucose levels of the patients with diabetes mellitus were proportional to clinical severity of the disease. After glucose loading, increments of blood sugar concentration were 2 or 3 times greater in the patients with diabetes

The diet of the patients was not restricted, and, except that 3 received intramuscular injections of iron, no medication other than prednisolone was given. A large initial dose was the quickest way of controlling the symptoms, the optimum for most patients being 10 mg. 4 times a day. Occasionally an even higher initial dose may be necessary. On this dosage, improvement is to be expected within 1 to 3 weeks, and thereafter the dose should be gradually reduced. The lowest maintenance dose reached in this series was 5 mg. daily, taken by some patients as 2.5 mg. twice daily, by others as 5 mg. each night.

It was found that long-term continuous treatment with prednisolone successfully induced a remission of the disease in every case. Threatened relapses were invariably aborted by a temporary increase in dosage, and so far, with the period of observation ranging from 18 months to 2½ years, the 17 patients still on a regular maintenance dose remain well. It is possible to tell the patient confidently that within a week or two of starting to take the tablets the symptoms will begin to subside.

PATHOLOGY

Evaluation of Lipoid Pneumonia. R. H. Sundberg, K. E. Kirschner and M. J. Brown. Dis. Chest 36:594-601 (Dec.) 1959 [Chicago].

The authors distinguish 2 main types of lipid pneumonia, which differ in causation and pathogenesis, namely, exogenous lipid pneumonia manifested by paraffinomas or oil granulomas due to aspiration of mineral oil, vegetable oil, or animal oil; and endogenous lipid pneumonia, such as cholesterol pneumonitis and Wegener's granulomatosis, resulting from metabolic, allergic, neoplastic, inflammatory, embolic, or toxic reactions within the lung tissue. In 4 of 13 patients with the diagnosis of lipid pneumonia, who were observed at the Mercy Hospital in San Diego, Calif., a history of long use of mineral oil, either in nose drops or for treatment of constipation, and the finding of oil droplets in the sputum of 3 of these 4 patients, formed the basis for the clinical diagnosis of lipid pneumonia. The other 9 patients were subjected to lobectomy or pneumonectomy and a pathological diagnosis of lipid pneumonia was made. The condition of all these patients had been previously classified as oil granuloma or paraffinoma.

The gross appearance of the lesions in the exogenous and in the endogenous type may look alike to the casual observer. In 4 of the 9 patients the classification of exogenous lipid pneumonia or paraffinoma secondary to the use of mineral oil was substantiated. In the other 5 patients, however, microscopic examination revealed endogenous, rather than exogenous, lipid pneumonia. The histological criteria for differentiation of the endogenous and exogenous types of lipid pneumonia are marked. In the presence of oils or paraffins, the macrophages present a honeycombed, vacuolated cytoplasm, which on special stain reveals large fat droplets. If cholesterol is present, the macrophages show a granular, foamy cytoplasm; special stains show fine punctate fat droplets within the cytoplasm.

The source of exogenous lipids is obvious; the cause of cholesterol deposits is more difficult to evaluate. It seems likely that many cholesterol granulomas are absorbed spontaneously and only those lesions persist which have met with severe desmoplastic reaction. These may require thoracotomy if extensive cavitation occurs. Diagnosis of lesions of an exogenous nature may be established by repeated analyses of sputum and by special staining techniques; a history of the use of oils may support the diagnosis. Treatment of patients with exogenous lipid pneumonia consists of discontinuing the use of the offending oil; rarely is surgical removal of the lesions necessary.

Hypoglycemia in a Case of Massive Fibrosarcoma (Mesenchymoma). J. Pedersen, F. Lund and J. Ringsted. Nord. med. 62:1642-1644 (Nov. 12) 1959 (In Danish) [Stockholm].

Grave hypoglycemic attacks may occur in cases of massive retroperitoneal tumors of fibrosarcoma character. The syndrome has been known for only 2 or 3 decades. In a case of severe hypoglycemic attacks in a woman, aged 71 years, with typical Wilson triad and typical electroencephalographic changes, the symptoms disappeared after removal of a retroperitoneal tumor weighing 1,010 Gm. (2¼ lb.). No insulin could be found in the tumor. Twelve well-documented cases are tabulated. The tumors weighed from 700 to 4,700 Gm. (1¾ to 10½ lb.) and were localized either retroperitoneally or, less often, immediately above the diaphragm, and were fibrosarcomas of low degree of malignancy. The pancreas was normal. The mechanism of the hypoglycemia is not known. The tumors do not cause hypoglycemia until they have reached a certain size. It is suggested that they may produce a substance with insulin activity.

Experimental Production of Atheromatous Embolization. L. B. Otken Jr. A. M. A. Arch. Path. 68:685-689 (Dec.) 1959 [Chicago].

The author recently observed at the Institute of Pathology of the University of Tennessee, in Memphis, 3 cases in which atheromatous embolization was an incidental finding. In all 3 instances there was a severe, generalized atherosclerosis, with ulceration of numerous plaques in the aorta. The cause of death was myocardial infarction in the first 2 cases and carcinomatosis from carcinoma of the men and 15 women) for from 3 to 11 weeks. Six of the 25 patients received hydrochlorothiazide in addition. The blood pressure fell in all but one patient. The hypotensive effect is long-continued and predominantly postural. In 18 cases the blood pressure is now considered to be satisfactorily controlled.

Symptoms of severe hypotension as well as side-effects were common early in the trial, when guanethidine was often given in doses exceeding 60 mg. daily, but recent experience has suggested that dosage of this order will seldom be required. Side-effects ceased to be troublesome when treatment was started with 10 or 20 mg. of guanethidine daily, the dose being subsequently increased by not more than 10 mg. at weekly intervals. The hypotensive action of guanethidine appears to be due to selective blockade of the sympathetic nervous system. Guanethidine reduces blood pressure by progressive stages. It is easy to administer, and the trial has shown that, with suitable precautions, it can be employed in the treatment of hypertensive patients.

Chloroquine Phosphate (Aralen) in the Long-Term Treatment of Rheumatoid Arthritis. J. P. Young. Ann. Int. Med. 51:1159-1178 (Dec.) 1959 [Lancaster, Pa.]

Young describes the results obtained in 50 consecutive private patients with chronic rheumatoid arthritis, who received the antimalarial drug, chloroquine (Aralen) phosphate, as the major medical agent in the management of arthritis for 18 to 36 months. Forty-four of the patients experienced a major improvement or complete remission; 2, slight improvement; and 4, no improvement. The improvement was sustained for as long as 36 months, without evidence of recurrence of symptoms or weakening of grip strength, such as occurs during long-term steroid treatment. Treatment with chloroquine was followed by a return to normal of sedimentation rates and hematocrit readings in a much higher percentage of patients than occurred in series treated solely with anti-inflammatory agents, such as steroids, phenylbutazone, and aspirin. The improvement in both the sedimentation rates and the hematocrit readings was found to be highly significant statistically. The rate of bone destruction found on roentgenologic examinations of the hands at yearly intervals was significantly less than that occurring in groups of patients treated by other methods. The clinical pattern of response follows a sequence similar to that observed in patients undergoing a spontaneous remission in arthritis. The type of improvement resulting from treatment with chloroquine suggests that this drug does not act simply as an anti-inflammatory agent, but influences some more basic feature of the disease.

An individualized dose schedule for chloroquine was employed, according to which treatment was begun with 125 mg. 3 times a week. Treatment was begun with a smaller dose (less than 375 mg. per week) only in patients who did not tolerate this dose. The initial dose was adhered to from 2 to 13 weeks. The goal was to achieve some subjective and objective improvement during the first 3 to 6 months of treatment while keeping the incidence of side-effects at a minimum. If this was accomplished, continuation of the same dose of chloroquine was usually found to lead to good symptomatic relief in another 6 months. If symptomatic relief was not complete after 6 months on a dose that had at first produced an improvement, the dose was raised to the next level for another 6 months. In each group of patients raised a step in the dose schedule, some persons developed symptoms of chloroquine intolerance. Therefore, all increases in dosage were made slowly and cautiously. The successive steps, after the initial 375 mg. per week, were 750 mg., 1.5 Gm., 2.25 Gm., and 3 Gm. per week, in divided doses 3 or 6 times a week. When chloroquine was given according to this dose schedule, side-effects were minimal in number, minor in degree, and reversible in character. Treatment with chloroquine is only one-third to one-half as expensive as treatment with steroids or phenylbutazone. In order to obtain the full benefit of chloroquine, its administration must be continued for more than 18 months.

Continuous Use of Prednisolone in the Treatment of Ulcerative Colitis. A. M. Gill and W. I. Kenyon. Am. J. Gastroenterol. 32:701-707 (Dec.) 1959 [New York].

In January, 1957, an investigation was begun to determine the results of long-term continuous treatment with prednisolone in a series of patients with ulcerative colitis. The series comprised 19 patients, 4 males and 15 females, their ages ranging from 19 to 77 years. It is of particular interest that one man, originally included, who showed no response to prednisolone, was found at laparotomy to have regional ileitis (Crohn's disease). The ulcerative colitis was severe in 12 patients, moderate in 2, and mild in 5. Those with the severe form had 6 or more motions daily with blood, tachycardia of 90 per minute or more, anemia, and raised erythrocyte sedimentation rate of 30 mm. or more; those with the mild form had 4 or less motions daily and no fever, anemia, or tachycardia; in those with the moderate form the symptoms were of intermediate degree. Eleven patients were in relapse, of whom 2 had had no previous treatment; 8 were new cases. Nine patients had been treated with corticotropin (ACTH) or with cortisone, but 6 had shown no response and the other 3 had had a relapse after a remission.

The Mechanism of Histamine Ulceration in the Guinea Pig. J. Watt. Gastroenterology 37:741-759 (Dec.) 1959 [Baltimore].

Although histamine ulceration can be produced in various species of animals, opinions vary regarding the pathogenesis of the ulcerative process. While some investigators favor the acid theory, others emphasize the vasodynamic and angiotoxic effects of histamine. The author suggests that both schools of thought might be correct in that ulcer pathogenesis differs in different species of animals; in one species histamine ulcerogenesis may depend upon the relative sensitivity of or damage to the vascular system, and in another species upon the degree of activity of the acid-secreting cells of the gastric mucosa.

The author studied the mechanism of histamine ulceration in the anesthetized guinea pig by continuous observation of the stomach wall under the dissecting microscope and by biopsy of lesions at various stages in their formation. Four stages in the acute ulcerative process are described: (1) the initial ischemic stage, in which there are focal irreversible degenerative changes in the mucosa, and also focal vasospasm of capillaries and arterioles; (2) a temporary reflow of blood, followed almost immediately by stasis; (3) a stage of hemorrhagic infarction; and (4) the final stage of ulceration by separation of the hemorrhagic necrotic tissue. The penetration of acid gastric juice into the mucosa is the primary etiological factor in initiating the acute ulcerative process. The focal ischemia of the first stage is secondary and incidental to the action of acid juice on the tissues.

It is believed that, in the guinea pig, histamine ulceration of the stomach results more from the excessive production and prolonged action of acid juice than from the degree of acidity reached in the gastric contents. Disturbances of cell metabolism may facilitate the entry of acid juice into the mucosal cells. In many examples of multiple acute ulceration of the stomach, both in man and in experimental animals, the earliest recognizable lesion is a focus of ischemic necrosis of mucosal cells, and it is largely on this morphologic feature that the spasmogenic theory of ulcerogenesis is based. This theory is criticized in that it has never been shown that focal ischemia of the gastric mucosa can occur in the absence of acid juice. In contrast, the morphologic picture is much more simply explained by the new concept that has emerged from the present investigation, namely, that the focal ischemia is a secondary effect due to the irritative action of acid juice on the mucosal vessels. It is concluded that this new role assigned to the acid gastric juice in the pathogenesis of multiple acute ulceration must strengthen one's faith in that time-honored dictum, "No acid, no ulcer."

Metastatic Carcinoma in the Cirrhotic Liver. B. Chomet, J. Valaitis and G. Pearah. Am. J. M. Sc. 238:753-759 (Dec.) 1959 [Philadelphia].

The authors discuss the rarity of coexisting hepatic metastases and cirrhosis. Twenty-five cases of this combination are recorded in the literature. Three cases seen by the authors are added to the small series so far published. Some authors hesitate to include biliary cirrhosis and metastatic hepatic carcinoma in a report of this combination, feeling that it is impossible to rule out the development of hepatic metastasis prior to the development of biliary cirrhosis. One of the 3 cases presented by the authors shows that a similar problem may exist in postnecrotic cirrhosis. The probable causes for the rarity of the combined condition, as defined by the different authors, are evaluated. It is curious to note that primary carcinoma of the liver and hepatic metastases show an inverse ratio. However, it is felt that the extreme rarity of coincident metastatic hepatic carcinoma and cirrhosis is a phenomenon still unexplained.

Recurrent Liver Cell Adenoma. S. W. Berkheiser. Gastroenterology 37:760-765 (Dec.) 1959 [Baltimore].

There is little information about the incidence and the prognosis of liver-cell adenoma. The incidence cannot be estimated, because in reported cases the differentiation among nodular regeneration, with or without cirrhosis, hamartoma, and adenoma is not always well defined. The author presents the history of a 71-year-old woman who was hospitalized because of vague abdominal discomfort and rectal bleeding. Roentgenograms of the abdomen disclosed an oval soft tissue mass in the right side of the abdomen. Exploratory laparotomy disclosed a large encapsulated tumor arising from the lower margin of the right lobe of the liver. The tumor with a wedge of normal-appearing liver was resected. The rectal bleeding was attributed to diverticulosis of the colon. The patient recovered. The microscopic study of the neoplasm revealed that it was composed of uniform large polygonal cells with eosinophilic cytoplasm and fairly regular nuclei. Individual cells resembled well-differentiated liver cells. Some of the cells were large with hyperchromatic nuclei, but abnormal mitotic figures were not observed. The absence of portal triads and central veins was striking.

The woman remained in good health for 6 years. Then she noted a lump in the left side of the abdomen which gradually increased in size. Laparotomy revealed a 12-cm. mass arising from the outer margin of the right lobe of the liver. The lesion together with a portion of the right lobe of the liver was resected. Another smaller mass to the left prostate in the third. There was nothing, either clinical or pathological, which could definitely be related to the finding of atheromatous embolization. Emboli were seen in the spleen, pancreas, kidneys, small intestine, and adrenals in the first case, in the spleen only in the second, and in the spleen and kidneys in the third. The small arteries showing the emboli were characterized microscopically by slit-like spaces surrounded by fibrous tissue, which had filled the lumen partially or totally. Occasionally, foreign-body giant cells were seen adjacent to the slits, which contained a substance readily identified as cholesterol with use of polarized light on frozen sections. The crystals were sometimes seen protruding into the media of the vessels. Scattered mononuclear cells were seen around some of these arteries. In the third case some arteries were seen to have the characteristic acicular spaces, but the spaces were seen to contain blood cells. The last observation suggested that the cholesterol crystals disappeared in some fashion, leaving only an imprint in the vessel.

In order to study the pathogenesis of atheromatous embolization, emboli were produced experimentally in rabbits by injecting human atheromatous material into the cardiac ventricular cavities. The animals were killed from one day to one month after the injection. Reactions to the emboli were twofold. Emboli of mixed constituency were associated with a panarteritis with many eosinophils, and these emboli organized very slowly. Single-cholesterol-crystal emboli were associated with a rapidly developing foreign-body reaction, becoming very difficult to find after only a few days' time, and finally not being found at all. It is suggested that atheromatous embolization occurs more commonly than is suspected but that the cholesterol crystals are rapidly converted into a soluble state and disappear. The emboli are apparently innocuous in the majority of instances.

Bacteriology of Lower-Respiratory-Tract Secretions, Sputum, and Upper-Respiratory-Tract Secretions in "Normals" and Chronic Bronchitics. A. W. Lees and W. McNaught. Lancet 2:1112-1115 (Dec. 19) 1959 [London].

Careful sampling methods of the bacteriology of sputum may be a misleading guide to the bacteriology of the bronchial tree, since sputum may be contaminated with upper-respiratory-tract secretions. Specimens of bronchial secretions, sputum, and upper-respiratory-tract secretions were obtained from symptomless patients with minimal pulmonary tuberculosis and from patients with chronic bronchitis. These were cultured, so that the results might be compared. Specimens of bronchial secretions were recovered by bronchial swabbing, a special technique being used to prevent contamination of the swabs with upper-respiratory-tract secretions Fourteen patients with small, healing, tuberculou lung lesions and 28 patients with chronic bronchiti were studied. The tuberculous patients were symptomless, and are referred to as normal.

Bronchial secretions in the normal subjects were sterile, but in patients with chronic bronchitis the sputum commonly contained potential pathogens-predominantly Hemophilus influenzae and Diplococcus pneumoniae. H. influenzae and D. pneumoniae were frequently found in the mouths and throats of both normal and bronchitic subjects These organisms were also found in sputum from normal subjects, and as they were not present in bronchial secretions, their source must have been the upper respiratory tract. Because of the liability to contamination with upper-respiratory-tract secretions, the bacteriology of sputum does not necessarily reflect the bacteriology of the bronchial tree organisms can confidently be regarded as originating in the lower respiratory tract only if they cannot be cultured from the upper tract. But organisms in the lower respiratory tract are so often present in the upper that culture of both sputum and oropharyngeal secretions would appear to have little practical value.

Extracervical Cancer Detections by Fluorescent Cytology: A Preliminary Report. De W. T. Hunter, D. N. Brown and R. F. Redmond. J. Oklahoma M. A. 52:772-777 (Dec.) 1959 [Oklahoma City].

The authors report on 5 men and 1 woman, between the ages of 48 and 68 years, in whom extracervical malignancy was detected by a fluorochrome fluorescent technique. Specimens which were collected by superficial scraping or which consisted of cell-rich secretions were smeared directly on albuminized slides. Cavity fluid and urine specimens were centrifuged and processed immediately without fixation. Staining for the fluorescent method was performed by immersing the hydrated slide in 0.01% acridine orange followed by 2 rinses in M/15 phosphate buffer and an interval in M/10 calcium chloride to enhance differentiation. The preparation was immediately scanned microscopically with an ultraviolet light source and appropriate filters. Transitional cell carcinoma of the urinary bladder was diagnosed in 2 of the 6 patients, primary carcinoma of the liver in 1, metastatic carcinoma with sarcoid reaction of the pleura in 1, basal-cell carcinoma on the dorsum of the neck in 1, and bronchiogenic carcinoma in 1. This new method of cancer detection seems at the present time to offer greater reliability and enables earlier detection of malignancies than is realized by conventional cytological techniques. Its application in the fields of bacteriology, mycology, virology, hematology, parasitology, and radiology are cited briefly.

BOOK REVIEWS

Treatment of Cancer in Clinical Practice. Edited by Peter B. Kunkler, M. A., M.D., M.R.C.P., Radiotherapist, United Birmingham Hospitals, Birmingham, and Anthony J. H. Rains, M.S., F.R.C.S., Professor of Surgery, University of London, London. Cloth. $19. Pp. 821, with illustrations. Williams & Wilkins Company, 428 E. Preston St., Baltimore 2; E. & S. Livingstone, Ltd., 16 & 17 Teviot Pl., Edinburgh 1, Scotland, 1959.

This book was written by 52 British authors and directed mainly to persons preparing for postgraduate examinations such as those for the F. R. C. S., M. R. C. O. G., and F. F. R. The editors hope that it may appeal to general practitioners as well as to specialists. To the former, it affords easy and medically entertaining reading. It is questionable if specialists would find the work worthwhile.

Each chapter deals with a general subject or broad principles or with a special region or subject in the field of clinical cancer. Practically all forms of cancer receive some consideration. The general purpose seems to be to discuss cancer therapy. There is disproportion among some of the chapters; for example, 13 pages are devoted to the whole field of tumors of the brain and spinal cord, 6 pages to the groin (essentially a discussion of lymphadenectomy in this region), and 23 pages to the rectum and anus. Possibly this is due to the fact that most readers will not be specialists but most likely general surgeons or gynecologists.

A great deal of stress is placed on radiation techniques for various growths which fall within the province of specialists in radiation therapy. There are many illustrations of radium applicators and roentgenograms showing radium needles or radioactive seeds in place. It is doubtful that the neophyte can judge which system is the best.

From the general viewpoint of teachers a number of objections and criticisms may be made. In discussing cholecystenterostomy, it is stated that "the opening need not be large—about 1 cm. in diameter (page 506)." This favors ascending cholangitis, and the modern concept is that the openings should be as large as possible, at least 2.5 cm. in diameter. In this textbook on the treatment of cancer only one paragraph (page 508) is devoted to primary cancer of the liver, and elsewhere only brief passing mention is made of liver resections; yet, there are over 1,000 reports in the international literature on liver resections for tumor, and there is a recent general surge of interest in total hepatic lobectomies (and already five-year results are recorded).

There has been some padding throughout this work by indulgence in discussion of extraneous material not directly concerned with the treatment of cancer, such as general surgical principles (thoroughly and repeatedly covered in numerous works on this subject), blood replacement, and fluid balance, in connection with operations, even to the point of setting down a series of platitudes in connection with postoperative care and mentioning that (page 660) "the sister in charge of the ward (who comes to the theater for her case) goes over these notes and may ask for further details."

The discussions on physics, principles, and methods of radiotherapy; aspects of the chemotherapy of malignant disease; and hormone control are well done and deserve commendation as perhaps the best portions of the book. The volume is well bound, the paper is of high quality, and the print is large and easy to read. There are many original photographs, diagrams, drawings, and tables which are instructive and pertinent to the subject matter.

I believe that the work will not find a large audience in the United States because it does not offer something superior to publications already well known here, and it may appear quite incomplete and not up-to-date. It would not suffice for adequate preparation in the fields of neoplastic diseases for those expecting to pass their American Board examinations.

ALEXANDER BRUNSCHWIG, M.D.

Surgical Philosophy in Mass Casualty Management, with Detailed Notes on Practical Care. By Warner F. Bowers, A.B., B.Sc., M.D., Chief, Department of Surgery, Tripler U. S. Army Hospital, Honolulu, Hawaii, and Carl W. Hughes, A.B., M.D., Assistant Chief, Department of Surgery, and chief, General Surgery Service, Tripler U. S. Army Hospital. Cloth. $6.75. Pp. 204. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1960.

Here at last is a well-written document on a subject of great importance. The authors admit that it propounds some untested theories. Although we may all hope that they will never be put to a practical test, if the occasion should arise their prompt applications should prove of great value. Mass casualties do not arise only from air raids and the use of atomic missiles by hostile powers. The authors draw on past experiences in war and peace. An atomic war would, however, increase the magnitude of the disaster beyond anything with which we are now familiar. For this reason, mistakes would be even more serious than those observed in tornadoes, floods, and fires in the past.

In the presence of mass casualties large numbers of wounded must be cared for by a decreased number of trained persons with limited supplies. In a of the round ligament was also resected. The patient recovered. Microscopic examination of the tumors showed identical features closely resembling the changes observed in the adenoma resected 6 years previously. There would seem to be no doubt that the recurrent neoplasm is an adenoma of the liver rather than nodular hyperplasia or hamartoma. Histologically it fulfills the criteria summarized by Ackerman as necessary to establish the diagnosis, namely, a tumor composed of well-differentiated cells, the absence of portal triads and central veins, and the absence of vascular invasion. It would also appear that the lesion is benign, although the pathological differentiation of benign adenoma and hepatoma of malignant nature may not always be distinct. Even though the tumor recurred 6 years after initial removal, the lack of metastasis on both occasions and the subsequent course indicate that the lesion is benign.

A survey of an autopsy material of 2,176 cases demonstrated that these lesions are extremely rare. Three liver-cell adenomas were found during a 9-year period. Two of them occurred in patients with cirrhosis, and are probably more characteristic of regenerative nodules. The third, an adenoma of mixed-cell type, was found incidentally in an elderly woman. Because of the difference in malignant potentialities of the adenoma group, it is recommended that an attempt be made to differentiate adenoma from nodular regeneration and hamartoma.

RADIOLOGY

Skeletal Changes in Wilson's Disease (Hepato-Lenticular Degeneration). V. M. Rosenoer and R. C. Michell. Brit. J. Radiol. 32:805-809 (Dec.) 1959 [London].

The authors present radiologic findings in 10 patients with hepatolenticular degeneration (Wilson's disease). Seven of the 10 patients had wedging of the vertebral bodies in the lumbar or thoracic spine, with irregularity of the upper and lower margins. Bone fragmentation, characterized by irregularity and sclerosis of the subchondral bone, was seen in 4 cases and was most easily demonstrated in the wrists and elbows. Osteochondritis dissecans was seen in 3 patients: 2 of these showed the lesions on the medial femoral condyles, while the third patient had a large area of osteochondritis dissecans on the medial aspect of the talus. This condition has not been previously described in association with Wilson's disease. Osteoarthritis was seen in 4 patients unassociated with osteochondritis dissecans, and one of these patients was seen in the orthopedic department with multiple loose bodies and osteoarthritis in both knee joints. Bilateral patellectomy had already been performed. Osteoporosis of slight degree was seen in 4 cases, but gross changes of osteomalacia with Looser's zones, as described by Finby and Bearn in 1958, were not seen.

The principal skeletal changes in Wilson's disease are osteochondritis of the spine, marginal bone fragmentation, osteochondritis dissecans, osteoarthritis, and osteoporosis. Possible mechanisms for these changes are discussed in the light of the known metabolic disturbances. It is suggested that the bone changes may be related in part to a renal tubular anomaly; hyperaminoaciduria, glycosuria, hyperphosphaturia, hyperuricosuria, peptiduria, and proteinuria have been reported. This condition may be related to copper deposition in the kidney, which might interfere with transport mechanisms in the tubular epithelium.

Roentgenography and Biopsy in Mammary Cancer. S. M. Berger, H. Ingleby and J. Gershon-Cohen. Radiology 73:891-895 (Dec.) 1959 [Syracuse, N. Y.].

The authors studied the accuracy of preoperative roentgenologic diagnosis for mammary cancer in 525 patients who were operated on during the past 2 years because of reported benign, malignant, probably benign, or suspected malignant breast lesions. Of 234 patients reported to have benign breast lesions and who were operated on, roentgenologic diagnosis was correct in 229 (98%). Of 108 patients reported to have malignant mammary lesions and who were operated on, roentgenologic diagnosis was correct in 106 (98%). In 173 women who had lesions reported as probably benign by the roentgenologist, 91 were operated on, and in 83 (91%) the condition was found to be benign. Of 122 women in whom the radiologist could make no definite diagnosis but suspected cancer, 92 were operated on, and 48 (52%) were found to have malignant disease. Roentgenologic examination of the breast in this series was very accurate when there were clear-cut findings of a definite benign or malignant lesion, but it was less reliable when the roentgenologic findings were less clear-cut. Roentgenologic examination was more difficult in adolescents, and young adults, but easier in older patients who had larger and fatter breasts.

In another series of 209 consecutive cancers, 151 were diagnosed correctly by the surgeon, but the roentgenologist increased this number to 194. Roentgenograms uncovered relatively small lesions, and incidence of metastases in the axillary lymph nodes was less than in palpable lesions evident to the patient or the surgeon. Roentgenologic examination had been positive for growing mammary cancer from 1½ to 4 years before the lesions became evident to the patient or the surgeon in 16 patients with delayed operations. The authors suggest that diagnosis of early mammary cancer could be made more frequently if surgeons would routinely employ roentgenologic examination of the breast.

pharmaceutical dispensing. The book should be a valuable reference book for persons interested in the allied sciences as well as for the pharmacist.

JOHN HEFFERREN, Ph.D.

The Placenta and Fetal Membranes. Edited by Claude A. Villee. Contributors: Emmanuel C. Amoroso and others. Cloth. $10. Pp. 404, with 87 illustrations. Copyright by Association for Aid of Crippled Children, New York 17. Williams & Wilkins Company, 428 E. Preston St., Baltimore 2, 1960.

This book contains eight reviews written by outstanding authorities on different aspects of the placenta and fetal membranes, a report of a conference held in Princeton, N. J., devoted to a full discussion of current placenta research, a survey of the literature, a bibliography of more than 2,700 references, and a list of investigations of current research being conducted in the United States and abroad. The book is dedicated to George L. Streeter and George B. Wislocki. The eight reviews and the contributors are as follows: (1) Comparative Aspects of the Hormonal Function, by E. C. Amoroso, (2) Histophysical Considerations, by E. W. Dempsey, (3) The Placental Circulation, by E. M. Ramsey, (4) The Placenta as the Fetal Lung, by D. H. Barron, (5) Transmission of Antibodies from Mother to Fetus, by F. W. R. Brambell and W. A. Hemmings, (6) Placental Function and Fetal Nutrition, by J. Dancis, (7) Biochemical Aspects, by C. A. Villee, and (8) Pathological Aspects, by A. T. Hertig. Each review is an outstanding contribution.

There were 35 participants at the Princeton conference, some of them from abroad, but each one an internationally known investigator. This book contains information about every aspect of the placenta and the fetal membranes. The bibliography consititutes an attempt to provide investigators with a list of material published since 1946 describing research on the placenta and fetal membranes. This encyclopedia should be in every medical library in the world and should be read carefully by every embryologist, anatomist, physiologist, pathologist, obstetrician, gynecologist, biochemist, and endocrinologist and by many other specialists as well.

J. P. GREENHILL, M.D.

Handbook of Diet Therapy. Written and compiled by Dorothea Turner for American Dietetic Association. Third edition. Cloth. $5. Pp. 222. University of Chicago Press, 5750 Ellis Ave., Chicago 37; Cambridge University Press, Bentley House, 200 Euston Rd., London, N. W. 1, England; University of Toronto Press, Toronto 5, Canada, 1959.

This book is based on the modern concept that therapeutic diets should be conceived as variations of the normal diet. The object of any therapeutic diet is to help to return the patient to normal life and normal nutrition. Basing therapeutic diets on the normal diet permits adaptations to suit those factors that influence food preferences. The author has pointed out that relatively little is known of nutrient requirements in disease. Consequently, diets are designed to meet or exceed the recommended dietary allowances of healthy people. This book presents dietary principles and concepts with sufficient illustrations and suggestions to permit the modifications necessary to meet the need of the individual patient or the institution with numerous diet demands. The tables of food composition are useful as they are up to date and present essentially all of the information needed for diet design. This is a good reference book for physicians, dietitians, and institution managers.

Encyclopedia of Medical Syndromes. By Robert H. Durham, M.D., F.A.C.P., Physician-in-Charge, Division of General Medicine, Henry Ford Hospital, Detroit. Foreword by T. R. Harrison, M.D., Professor and Chairman, Department of Medicine, Medical College of Alabama, Birmingham. Cloth. $13.50. Pp. 628. Paul B. Hoeber, Inc. (medical book department of Harper & Brothers), 49 E. 33rd St., New York 16, 1960.

According to Himsworth, who is quoted in the front of this reference book, syndromes are rapidly replacing many "disease entities" in medical writing and thinking. A syndrome may arise from different causes. "It is rarely possible to define a disease precisely but it is always possible to characterize a syndrome." This book, which briefly describes about 1,000 carefully selected syndromes, fulfills a long-felt need. Probably the reason it was not written sooner is that an enormous amount of work is involved. Great credit should therefore go to the compiler. Although each description is necessarily brief, it includes, when pertinent, a list of synonyms and a statement about the incidence, sex ratio, congenital factors, cause, clinical manifestations, pathological findings, course, treatment, and prognosis, and bibliographic references.

All items are presented in alphabetical order including cross references to synonymous or related syndromes. Unfortunately the author prefers eponyms to descriptive titles. At first glance it might seem that an encyclopedia of this kind would not need an index, but the author has performed a valuable service by providing an index arranged by classification starting with "allergic syndromes" and ending with "urogenital system." This should be a great help in locating a syndrome the name of which has momentarily escaped the user. Once a physician, regardless of his special interest, has familiarized himself with this book he would probably not want to be without it.

W. G. BRANDSTADT, M.D.

disaster "our main business is not to see what lies dimly at a distance but to do what lies clearly at hand." The keynote is preparedness, and this implies realistic planning. Regardless of the nature of a disaster, organization is essential and military organization, having stood the test of time, should be used as a model.

After analyzing the problem in general terms the authors describe the characteristic effects of trauma, principles of sorting casualties, treatment groups, cost of delaying medical care, chemical and bacteriological warfare, lessons learned from civilian disasters and simulated casualty exercises, and the compromises required in mass casualty care. There is an index and a list of bibliographic references. Several typographic errors are noted, and it is hoped that these will be eliminated from future printings. This important book should be read by every physician, veterinarian, dentist, nurse, hospital administrator, and others whose role in handling mass casualties could be helpful. The authors are not alarmists but are keenly aware of the need for a realistic approach to an ever present problem.

W. G. Brandstadt, M.D.

Prosthetic Principles—Above Knee Amputations. By Miles H. Anderson, Ed.D., Director, Prosthetics Education Project, School of Medicine, University of California, Los Angeles, John J. Bray, C.P., C.O., Associate Research Prosthetist, Prosthetics Education Project, School of Medicine, University of California, and Charles A. Hennessy, C.P., C.O., Associate Director, Prosthetics Education Project, School of Medicine, University of California. Edited by Raymond E. Sollars, Associate Director, Prosthetics Education Project, School of Medicine, University of California. Cloth. $10. Pp. 331, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1960.

This book presents, in outline form, the fundamental techniques and principles for the proper fabrication and fitting of prostheses for the above-knee amputee. The teaching techniques were coordinated at the University of California in Los Angeles, but many of the basic principles were developed in the Prosthetics Research Project at the University of California in Berkeley and in other research units under the supervision of a committee of the National Academy of Sciences-National Research Council.

The publication is primarily a teaching manual for progressive prosthetists. It is not a comprehensive textbook, but the material covered is presented in a step-by-step manner with clear and concise illustrations. For physicians who are active in prosthetic clinics, it will be a ready reference for review of above-knee prosthetic principles and should lead to more complete understanding and cooperation with the manufacturing prosthetists in a given area. The effectiveness of the publication for physicians will depend on the degree of the physician's general knowledge of the prosthetic and amputee problem. It will be of little value to a physician who has not attended one or more of the prosthetic education courses that are now offered at New York University, the University of California in Los Angeles, and Northwestern University in Chicago. The chief value of the manual will be as a practical reference for the manufacturing prosthetists.

Clinton L. Compere, M.D.

Husa's Pharmaceutical Dispensing: A Textbook for Students and Teachers of Pharmaceutical Compounding and Dispensing and a Reference Book for Pharmacists in Retail and Hospital Pharmacy and in Pharmaceutical Development and Production. Editor: Eric W. Martin, Ph.C., B.Sc., M.S. Assisted by John E. Hoover, B.Sc. Fifth edition. Cloth. $12. Pp. 729, with illustrations. Mack Publishing Company, 20th and Northampton Sts., Easton, Pa., 1959.

On the title page it is stated that this book is "a textbook for students and teachers of pharmaceutical compounding and dispensing and a reference book for pharmacists in retail and hospital pharmacy and in pharmaceutical development and production." The text succeeds in fulfilling this difficult task.

The individual chapters were prepared by persons familiar with the specific areas and are documented with current references. In many cases books and specific published reports are suggested for general reference; thus, the book offers the reader an opportunity to study a particular area of interest to whatever depth he desires. Included in the text is information on the usual pharmaceutical dosage forms such as powders, capsules, tablets, pills, ointments, suppositories, suspensions, solutions, and emulsions. Throughout these chapters, information is included on the characteristics, trade names, and sources of the many products used as pharmaceutical aids in the manufacture of the finished product. Chapters on ear, eye, nose, and throat solutions; sterilization; coatings; drug stability; and prolonged drug action include useful information of current interest. Additional chapters discuss the activities of professional, hospital, governmental, dental, and veterinary pharmacies.

The chapters on inorganic and organic incompatibilities cite many specific drug products as illustrations. These chapters contain lists of known compatibilities and incompatibilities as well as some of the ingredients of a large number of commercial drug products. This information should be extremely valuable when it is necessary to add an ingredient or to mix individual commercial drug products.

The title of the book may be too restrictive as the book includes a wider coverage of pharmaceutical information than is usually considered as

Unfortunately, the results are being communicated through personal contact or in small meetings of industrial research men."

There is no standard test or questionnaire which determines adaptability to a foreign environment. Of course, many tests and questionnaires exist in the area of aptitudes, personality, attitudes, interests, and race relations which could be fruitfully adapted to the purpose in question. Among these are the Strong vocational interests questionnaire, various foreign language aptitude tests, various tests of rigidity and ethnic attitudes, like the Sanford-Levenson scale, and measures of ethnocentrism and authoritarianism.

For specific references on tests and questionnaires, see the "Fourth Mental Measurement Yearbook," ed. 3, edited by O. K. Buros, Highland Park, N. J., Gryphon Press, 1953.

UNILATERAL CHRONIC UVEITIS

To the Editor:—*Five years ago a young woman developed iridocyclitis associated with corneal ulcer which was apparently precipitated by exposure to cold and camp-fire smoke during a hunting trip. She has received all the usual local and systemic treatments, but a haziness of one cornea, postcorneal deposits, and a marginal iritis still persist. Her general physical condition is excellent. She has been under the care of competent ophthalmologists. Suggestions for continued treatment of this patient will be appreciated.*

Samuel H. Worthen, M.D., Afton, Wyo.

Answer.—It is presumed that in this patient only one eye is affected and that the other one is normal. Since unilateral chronic uveitis is rarely associated with systemic disease, it may be more profitable to look in the eye itself for such factors as intraocular foreign bodies, external local tissue, infection by fungus or other micro-organism, neurogenic reaction, and possibly a low-grade malignant growth. Biomicroscopic examinations of the cornea and anterior segment of the eye, if done frequently, may reveal phases of intensity of the cellular reaction; cultures of the aqueous humor and microscopic examination of stained cells from the anterior chamber may be sources of information. A well-established etiological and therapeutic procedure is an iridectomy, with careful microscopic examination and culture of the removed section of the iris.

Treatment should be based on ocular findings alone, and often the administration of systemically given steroids may be more harmful than helpful. Hence it would be well to discontinue all systemic treatment for about one year and depend on local instillation of mydriatic, astringent agents, local heat, and protection from bright lights. A complete series of allergenic skin-reaction tests may indicate sources of systemic involvement not hitherto revealed. Supplies of antigens for such tests are usually available in the clinics of large hospitals.

AXILLARY ABSCESS

To the Editor:—*Is there a possible relationship between a lung abscess and a primary apocrine gland abscess in the axilla that occurred after granulomatosis due to use of a deodorant containing zirconium?* *M.D., West Virginia.*

Answer.—There appears to be no method of securing definitive proof that a given pulmonary staphylococcic abscess has arisen as a result of an abscess in the axilla. One's suspicion would undoubtedly be aroused by the sequential development of pulmonary abscesses after hidradenitis suppurativa. However, such a sequence is not generally known to occur. Granulomas due to zirconium are not commonly associated with axillary abscesses. One might culture the organisms from both the axillary and pulmonary abscesses. If bacteriophage typing and multiple-colony antibiotic-sensitivity tests demonstrated that the organisms were of identical strain, this would be suggestive, although far from firm proof, that the pulmonary lesions were of metastatic origin.

With regard to the second question, Shelley and Hurley have presented data which would indicate that the zirconium granuloma is an allergic reaction involving the reticuloendothelial system. It is presumed that this hypersensitivity is not limited to the skin. At the time of writing there are no reports of systemic zirconium granulomatoses. The possibility exists, however, that in allergically sensitized persons "zirconiosis" might occur as a counterpart to zirconium granuloma of the skin, just as berylliosis may be conceived as a counterpart to beryllium granuloma of the skin. Finally, it should be stressed that, in the normal, nonsensitized person, zirconium is completely innocuous.

DIAGNOSIS OF MONGOLOID CONGENITAL DEFECT

To the Editor:—*It has been my privilege to provide obstetric services for some families of Asiatic origin. The problem that confronts me is how to recognize fetal abnormalities—in other words —to recognize a mongoloid idiot in a family from Outer Mongolia.*

Willard Crosley, M.D., Glendale, Calif.

Answer.—The mongoloid facies, although a most important finding to alert the physician that a newborn child may have mongolism, is not necessarily the most important diagnostic finding. Additional signs to look for are hypotonicity; poor vascular tone; the presence of congenital heart defects; abnormal palmar markings; speckled iris; abnormally small, curved fifth digit, with hypoplasia of the

QUESTIONS AND ANSWERS

CARBON MONOXIDE POISONING

To the Editor:—*A method of treating victims of carbon monoxide poisoning which should not be beyond the resources of small municipalities is the use of a recompression chamber such as is commonly used in the treatment of divers with caisson disease, or the "bends." Has this possibility been investigated, and, if so, what are its capabilities and its limitations?*

Alfred B. Mason, M.D., Concord, Calif.

Answer.—It has been demonstrated that the use of high partial pressures of oxygen in the treatment of carbon monoxide poisoning is of considerable benefit. Ideally, the patient should receive the highest partial pressure of oxygen that can be administered short of producing actual oxygen toxicity. A suggested treatment schedule for a patient with severe carbon monoxide poisoning would be administration of 100% oxygen by mask in a recompression chamber, at a gauge pressure of (1) 25 lb. per square inch for 20 minutes; (2) 15 lb. per square inch for 20 minutes; and (3) 5 lb. per square inch for 90 minutes, followed by six hours or more of treatment with 100% oxygen at normal atmospheric pressure. This regimen should supply the patient with a plasma-oxygen level sufficiently high for all tissue needs for the two-hour period during which about 75 to 80% of the carbon monoxide will have been eliminated. It is important to remember that an increase in either the partial pressures or the time exposures beyond this suggested schedule may cause the patient to have severe convulsions due to oxygen toxicity. This can be reversed by removing the supply of 100% oxygen and substituting atmospheric air for breathing.

Answer.—To be revived, the heart action of the victim of carbon monoxide poisoning must be adequate to circulate the blood, even though he may not be breathing. Administration of 100% oxygen combined with artificial respiration, to dispatch the gas to the pulmonary alveoli, will initiate the dissociation of carbon monoxide from hemoglobin and ventilatory elimination, because the partial pressure of oxygen (after one or two breaths) will be at least 300 times that of carbon monoxide. The blood, as it leaves the lungs, will have about 1.5 vol.% of oxygen in physical solution, and the hemoglobin will combine with a considerable amount of oxygen as well. The carbon monoxide will be effectively removed from the patient within a short time. Oxygen, readily available, is the treatment of choice.

The same partial pressure of oxygen could be provided to the patient by placing him in a compression chamber at 5 atmospheres of air pressure, but this procedure would be difficult and more time-consuming. Administration of oxygen at a pressure of more than 1 atmosphere of oxygen would increase the speed of carbon monoxide-hemoglobin dissociation, but when given at such pressure oxygen becomes increasingly toxic to the patient. A compression chamber is, apart from its expense and operating difficulties, a less efficient and less safe treatment for carbon monoxide poisoning. Any delay in increasing the partial pressure of oxygen is undesirable; oxygen equipment can be taken to the victim, whereas he would have to be taken to a compression chamber.

PSYCHOLOGICAL EVALUATION FOR FOREIGN DUTY

To the Editor:—*Industries with holdings on several continents often transfer their personnel from one country to another, sometimes for prolonged periods. Appraisal of the psychological adaptability of the person being assigned to a foreign environment would be beneficial to both employer and employee. Is there a questionnaire or some similar form of examination that will provide such an evaluation and could be used by the general practitioner or industrial physician?*

Harold E. Reed, M.D., Akron, Ohio.

Answer.—There are few references in the literature on the appraisal of psychological adaptability to a foreign environment. A primary reference is "Assessment of Men" (OSS Assessment staff, New York, Rhinehart & Company, Inc., 1948). This book includes a number of techniques for evaluation of suitability of personnel for overseas assignment which are designed for use by a United States government agency rather than an industrial corporation.

Possibly a good deal of work has been done in this area which has not been published. According to Kendall, "A substantial amount of the work being done in industry is not finding its way into the traditional publication outlets. . . . Some excellent work is being done by psychologists in industry.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

WASHINGTON NEWS

Political Moves on Aged Bills . .
U. S. Workers' Health Insurance . .
Isolation Problem of Aged . .
Pathologists to Advise on Air Crashes . .

CONGRESS DEBATES ISSUE OF AGED HEALTH

The Eisenhower administration disclosed that it would dispatch to Congress soon an alternative measure to the controversial Forand proposal that would provide medical and hospital benefits to social security beneficiaries.

The announcement came after the House Ways and Means Committee defeated the Forand legislation by a 17-to-8 vote. However, Rep. Aime Forand (D., R. I.), sponsor of the bill, filed a discharge petition in a seldom-tried maneuver to force a vote on the bill by the full House despite the adverse Committee action. A majority of the House membership—219 members—must sign such a petition in order to bypass the Committee.

Arthur S. Flemming, Secretary of Health, Education, and Welfare, said the administration plan will involve federal payments to the states to help subsidize purchase of private health insurance by needy elderly persons. He said it would be voluntary.

Another plan was being considered by some lawmakers of both parties. Under this approach, existing federal payments to the states for public assistance would be increased, perhaps by 200 million dollars or more, to spur medical programs for the needy aged through existing aid mechanisms.

Support for the Forand measure was voiced by three leading candidates for the Democratic presidential nomination—senators John Kennedy (Mass.), Hubert Humphrey (Minn.), and Stuart Symington (Mo.)—who told a labor rally in Detroit that they would work for its passage.

On the other hand, President Eisenhower and Vice-president Richard Nixon renewed their opposition to any compulsory health plan. Mr. Eisenhower told his weekly news conference that the Forand bill would be a definite step toward socialized medicine. Improved medical care for the elderly must be achieved through further development of voluntary health insurance programs, he said.

Vice-president Nixon made known in a letter to many physicians who had inquired about his position that he was unalterably opposed to any scheme that involved compulsion. The best solution, he said, was a program "which will enable those who desire to do so to purchase health insurance coverage covering catastrophic illnesses from private group carriers."

Meanwhile, Senate Republican leader Everett M. Dirksen (Ill.) criticized labor leaders for attacking the administration and the American Medical Association at hearings before the special Senate subcommittee on aging. United Auto Workers President Walter Reuther and President James B. Carey of the Electrical Workers Union contended that opponents of the Forand bill were callous and selfish. Dirksen said their remarks were "gratuitous slurs" constituting "an absolute disservice to the country." He noted that the administration and the medical profession have been bending every effort to improve the lot of the aged.

HEALTH INSURANCE FOR FEDERAL WORKERS

The federal government's major new health insurance plans for its employees were announced. Scheduled to start July 1, they will cover an estimated 4 million employees and their dependents, making the government-wide insurance set-up the largest voluntary plan in the world.

Previously, the federal government had not contributed to any employee health programs. Congress last year approved legislation to establish a contributory plan similar to those used in many private industries. The United States was expected to pay about 100 million of the 250-million-dollar annual cost of the program.

Two major plans agreed on were a Blue Cross-Blue Shield service program and a commercial indemnity plan. Aetna Life Insurance Company, main carrier for the private indemnity plan, was expected to ship out the actual underwriting to about 200 private carriers who have expressed interest in participating.

The health plans are both somewhat more liberal than many existing plans (for example, there will be no waiting period for maternity benefits), but otherwise are similar in benefits offered and premium costs for existing indemnity and service plans.

Under all the plans, including 38 smaller ones that are mainly variations of existing plans, tailored to meet new requirements and the government contribution, the government would pay the same amount—from $2.82 a month for single employees to $6.76 for an employee and his family. The cost of the indemnity plan will be somewhat less than the Blue Cross-Blue Shield option, but the benefits differ under the programs.

During the month of June government workers will make their individual choices about which of the proposed plans they want. Both major plans have high and low options, although the government contributions remains the same. Employees have to pay more out of their own pockets for the high options which offer greater benefits. Some details of the major options follow.

GOVERNMENT-WIDE INDEMNITY PLAN

The high option pays the first $1,000 of each calendar year's hospital room and board per person and 80% of any charge over that amount. For other hospital expenses as well as medical expenses, in-

(Continued on next page)

second phalangeal bone of the fifth digit; relative microcephaly; protruding tongue; short neck; laxity of skin; abnormally increased space between the first and second fingers and toes; and broad ilia. Although any of these findings may be present, none is pathognomonic. The differential diagnosis includes cretinism, which can easily be established. The epicanthal fold of a mongoloid idiot is different from that of a normal baby of Asiatic extraction and is confined to the inner angle rather than including all or most of the upper lid.

FINGERPRINTS OF INFANTS WITH MONGOLISM

To the Editor:—*I recently read that fingerprints of children with mongolism show characteristic changes which facilitate diagnosis. What information do you have on this subject?*

A. R. Stough, M.D., McAlester, Okla.

Answer.—Several aberrations of fingerprints have been found specifically in patients with mongolism. One is a triradius, which is a triangle formed by the junction of ridges coming from three directions placed centrally in the palm; a second is extreme transversability of the ridges in the distal part of the palm; and the third includes variable combinations of patterns on the distal phalanges.

About 70 to 80% of patients with mongolism will show some degree of these abnormalities, which can also be observed in a small percentage of normal persons. Hence, like most of the stigmata attached to mongolism, fingerprinting must be considered corroborative and not diagnostic. In the newborn period, when it would be most helpful, adequate prints are difficult to obtain.

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Cummins, H., and others: Palmar Dermatoglyphics in Mongolism, Pediatrics 5:241 (Feb.) 1950.

Walker, N. F.: Use of Dermal Configurations in Diagnosis of Mongolism, Pediat. Clin. North America, page 531, May, 1958.

HYPERTROPHY OF PAROTID GLAND

To the Editor:—*A male patient, aged 51 years, has noticed a bilateral, generalized enlargement of the parotid glands for at least three years. Palpation does not disclose hardness, pain, or evidence of inflammation. The man is tall and of average weight and has enjoyed good general health except for a fractured femur about six years ago. The patient is asymptomatic, except for the change in facial appearance. Before performing a biopsy on the gland, what other investigative studies should be done?*

G. K. Hammersley, M.D., Frankfort, Ind.

Answer.—A patient with a bilateral, generalized enlargement of the parotid glands of three years' duration probably has a benign condition. Chronic inflammation due to stones in both parotid ducts, hypertrophy of salivary glands (Mikulicz's disease), and leukemia could be ruled out by examination of the parotid duct for other glandular involvement and blood studies. Some men who gain weight in middle age tend to have a fatty infiltration in the region of the parotid glands which gives them a "chipmunk-like" protuberance in this area. Since, after three years, no masses are felt and the "swellings" are asymptomatic, no treatment is indicated for this patient.

UTERINE SUSPENSION

To the Editor:—*What are the indications for performing an operation for uterine suspension?*

M.D., New York.

Answer.—As knowledge of the anatomy and physiology of the female pelvic reproductive organs has increased, the indications for performing uterine suspension have diminished. This operation rarely is performed as a primary procedure.

Valid indications for uterine suspension are as follows: (1) uterine prolapse, retroversion, and other disturbances of the pelvic floor in a young woman; (2) retroversion resulting from chronic pelvic inflammatory disease in a patient in whom the uterus is to be conserved; (3) endometriosis, particularly when the lesions are present in the cul-de-sac or on the rectosigmoid, when the raw surfaces are to be kept away from the posterior surface of the uterus; and (4) third-degree retroversion with symptoms of dysmenorrhea and backache which is relieved by manual replacement of the uterus, followed by wearing of a pessary. (If the symptoms recur when the pessary is removed, shortening of the round ligament is indicated.) Uterine suspension is sometimes performed incidental to the removal of benign pelvic lesions, when a retroversion is present.

IDENTIFICATION OF SPERMATOZOA

To the Editor:—*How long can sperm remain in the vaginal canal and be identified by laboratory examination?* *H. J. Savage, M.D., Cleveland.*

Answer.—Motile spermatozoa have been found in the female genital tract as long as 28 hours after their introduction into the vagina. Motility commonly ceases within three hours. Identifiable nonmotile spermatozoa have been reported present in the vagina after 17 days. They have also been reported present for a maximum of only 45 minutes. No information on the persistence of nonmotile spermatozoa in the vagina of a non-nubile female is available. Such factors as vaginal flora, cervical secretion, exudate, physical activity, and douches have to be considered in each instance. Most of these do not pertain before puberty.

Under the program, the pathologist located nearest an accident will visit the scene as soon as possible. An on-the-spot inspection and other studies, performed in cooperation with local authorities, will attempt to determine any elements involving human factors. These would include a study of possible medical factors involving air crew personnel which may have contributed to the accident; correlation of these with the pattern of injury and death to determine the sequence of events which led up to the accident; and general medical data applicable to current safety rules and regulations of the Federal Aviation Agency. This approach has provided invaluable information in recent accident investigations, the FAA said.

The 21 consultants, all physicians, are Drs. Theodore J. Curphey, Los Angeles; Joseph H. Davis, Miami, Fla.; Donald K. Merkeley, Lewiston, Maine; Joseph E. Campbell, Chicago; William J. Reals, Wichita, Kan.; Nicholas Chetta, New Orleans; Irving I. Goodof, Waterville, Maine; Russell S. Fisher, Baltimore; Richard Ford, Boston; Edward S. Zawadski, Detroit; Angelo Lapi, Kansas City, Mo.; Lester Adelson, Cleveland; Leo Lowbeer, Tulsa, Okla.; Milton Helpern, New York; Joseph W. Spelman, Philadelphia; Vernie A. Stembridge, Dallas; Frederick Bornstein, El Paso, Texas; Robert Hausman, San Antonio; Geoffrey Mann, Richmond, Va.; Charles P. Larson, Tacoma; and B. C. Willard, Orlando, Fla.

MISCELLANY

Rep. Aime J. Forand (D., R. I.), sponsor of the controversial bill to provide federal health insurance for the elderly, announced that he will not run for reelection this fall. Forand, who has served in Congress since 1937, said health reasons prompted his decision. The lawmaker is second-ranking Democrat on the House Ways and Means Committee.

Rep. John Rooney (D., N. Y.) said that the failure of many exchange medical students to return to their countries after training in the United States defeated the purpose of the program, which is "to have these people go back to their countries and practice their professions . . . so that they would become pro-American minded in their activities in their field in their own country."

The House passed and sent to the Senate a resolution asking the President to call a White House conference on narcotics as a "focal point for a sustained attack on the problem" of addiction. The administration opposed the conference, contending that it would amount to a duplication of already available information.

The administration said it would pay 10 million dollars to cranberry growers who suffered losses through no fault of their own as a result of the barring of some shipments of berries contaminated with a weed-killer last fall.

PHS Surgeon General Leroy E. Burney urged unvaccinated persons to get their Salk poliomyelitis vaccine now. He noted that the Salk poliomyelitis vaccine is most effective if used before polio is prevalent in the summer months. "If demand for vaccine is low now, supplies are likely to be low in summer, since the present supply may be outdated by then," he cautioned.

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Facilities for complete and frequent blood counts must be available for patients receiving 'Leukeran', 'Myleran' or 'Purinethol'.

Full information about these products will be sent on request.

References: 1. Unugur, A., Schulman, E., and Dameshek, W.: New England J. Med. 256:727 (Apr. 18) 1957. 2. Burchenal, J. H., Karnofsky, D. A., Murphy, M. L., Ellison, R. R., Sykes, M. P., Tan, C. T. C., Mermann, A. C., Yuceoglu, M., and Rhoads, C. P.: Am. J. M. Sc. 228:371 (Oct.) 1954. 3. Altman, S. J., Haut, A., Cartwright, G. E., and Wintrobe, M. M.: Cancer 9:512 (May-June) 1956.

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Full information about these products will be sent on request.

References: 1. Ellison, R. R., and Burchenal, J. H.: J. Chronic Dis. 6:421 (Oct.) 1957. 2. Ultmann, J. E., Hyman, G. A., and Gellhorn, A.: J.A.M.A. 162:178 (Sept. 15) 1956. 3. Bethell, F. H.: J. Chronic Dis. 6:403 (Oct.) 1957.

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Tuckahoe, N. Y.

cluding operations, nursing care, and physicians' visits, the high option pays 80% of charges over the first $50 per person.

For maternity benefits, the high option pays $15 a day for 10 days for hospital expenses. The obstetrician receives up to $90 for normal delivery, $150 for cesarean, and $60 for miscarriage. Employees pay the rest. The anesthetist is paid up to $18 for normal delivery, $30 for cesarean, and $12 for miscarriage. The maximum benefit an individual person can receive is $30,000. The low option plan is similar but provides [illegible] including a $10,000 per person [illegible]

BLUE CROSS-BLUE SHIELD

Under the high option, all expenses for up to 120 days in the hospital are provided, including room, board, and other hospital services. On surgical and medical bills, all expenses are paid if the income is less than $6,000 a year (in Washington, D. C., area. This salary point varies according to different areas of the country). For employees earning more than a certain salary, physicians have the right to charge any additional amounts believed necessary.

The high option service plan would pay hospit expenses up to $100 for maternity cases pl amounts set by fee schedules (according to Bl Shield local schedules) for obstetrician and ane thetist.

After out-of-pocket expenses of $100 or more f uncovered services, the major medical portion of t plan covers 80% of all additional expenses up t maximum of $20,000. The low option plan, prov ing lesser benefits, has a maximum supplemen benefit of $5,000.

ISOLATION IS MAJOR PROBLEM OF AGED

American society's accent on youth has posed the major problem to older persons—their isolation from the rest of society—according to Dr. James Z. Appel, member of the Board of Trustees of the American Medical Association.

Testifying before the special Senate subcommittee on aging, Dr. Appel said that "until the people of this country abandon their misconceptions about aging, this isolation will continue."

"As long as our older people are thrust aside by a society which insists upon placing the accent on youth, a stream of lonely, idle, disheartened men and women will seek whatever emotional shelter they can find," he testified. "Too often, the only shelter available to them is the hospital, the nursing home, or the public institution."

Dr. Appel described the growth of voluntar health insurance as "little short of phenomenal" and said that "tremendous progress" also was bein made by voluntary action at the community leve throughout the United States.

"As physicians, we try to keep all of our patient out of institutions and functioning in society," Dr Appel said. "Our object is to help them lead lives a normal as possible."

AIR AGENCY APPOINTS PATHOLOGISTS FOR CRASH STUDIES

The Federal Aviation Agency named 21 of th nation's leading forensic pathologists as consultant to determine to what extent human factors ma cause airplane crashes.

MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. F. J. L. Blasingame, 535 North Dearborn St., Chicago 10, Executive Vice-President.
1960 Annual Meeting, Miami Beach, Fla., June 13-17.
1960 Clinical Meeting, Washington, D. C., Nov. 28-Dec. 2.
1961 Annual Meeting, New York City, June 26-30.
1961 Clinical Meeting, Denver, Nov. 27-Dec. 1.
1962 Annual Meeting, Chicago, June 11-15.
1962 Clinical Meeting, Los Angeles, Nov. 25-30.

AMERICAN

1960

April

ALABAMA, MEDICAL ASSOCIATION OF THE STATE OF, Admiral Semmes Hotel, Mobile, Apr. 21-23. Mr. W. A. Dozier Jr., 19 S. Jackson St., Montgomery 4, Executive Secretary.

AMERICAN ACADEMY OF NEUROLOGY, Eden Roc Hotel, Miami, Fla., Apr. 25-30. Mrs. J. C. McKinley, 4307 E. 50th St., Minneapolis 17, Executive Secretary.

AMERICAN ACADEMY OF PEDIATRICS, Atlantic City, Chalfonte-Haddon Hall, Apr. 20-22. Dr. E. H. Christopherson, 1801 Hinman Ave., Evanston, Ill., Executive Director.

AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE, SECTION ON MEDICAL SCIENCES, Vanderbilt University, Apr. 18-19. Dr. George R. Meneely, Vanderbilt University School of Medicine, Nashville 5, Tenn., Chairman.

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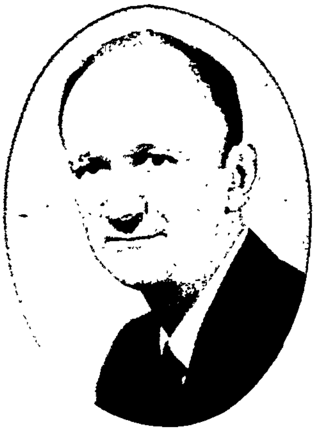

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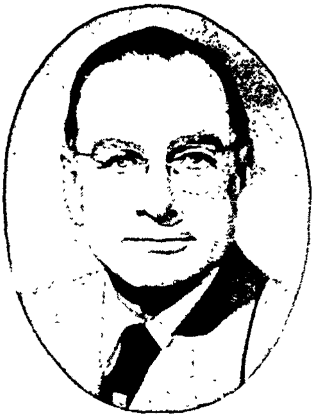

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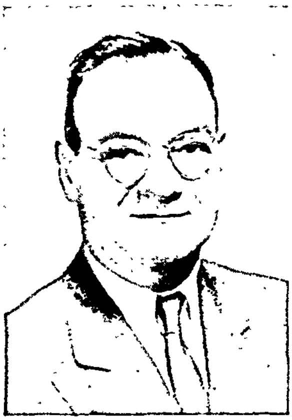

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SPREAD OF CANCER CELLS AND ITS RELATIONSHIP TO CHEMOTHERAPY

George E. Moore, M.D., Avery A. Sandberg, M.D.
and
Alvin L. Watne, M.D., Buffalo

Free cancer cells can be identified in the circulating blood by removing the erythrocytes with a heparin-fibrinogen mixture, centrifuging the plasma, and examining smears made from the buffy coat. In a series of 179 patients with advanced cancer, one-half of the samples of peripheral blood studied in this way yielded recognizable tumor cells. These metastasizing cells with diameters of 10 to 30 μ could deform and pass through apertures less than 10 μ in diameter and hence could traverse capillary beds. Washings of the peritoneal cavity before and at the end of celiotomy in patients with malignant intra-abdominal lesions similarly yielded tumor cells. These findings prove the need of care to prevent the iatrogenic spread of malignant cells. They also encourage the continued search for cytotoxic, anticancer agents that can be administered to patients with malignant disease to prevent metastasis.

CANCER usually kills by invading adjacent tissues, thereby interfering with normal physiology, and by metastasizing to distant sites where additional tumor cell replication occurs at the expense of the host. Surgery and irradiation provide adequate therapy for many malignancies which are characterized by long periods of local growth or by metastases confined to the regional lymph nodes. For this reason, knowledge of the patterns of regional lymph node metastasis has been of practical importance and, thus, the object of many investigations. In the past, the study of lymphatic metastases also predominated because histological techniques were available for sectioning lymph nodes and lymphatics containing tumor tissue.

In contrast, exfoliative cytology was not yet developed, and hence the direct contamination of body cavities, wounds, and fistulas with tumor cells was not studied intensively, although clinical observations of these modes of dissemination were common. Similarly, cancer cells were probably found in the blood by Ashworth as early as 1869, but systematic studies of the blood for tumor cells were first done by Pool and Dunlop[1] in 1934 and by Engell[2] in 1955. With the advent of cancer chemo-

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From Roswell Park Memorial Institute.

A correlation of histological evidence of the direct invasion of veins with malignant growths and the presence of tumor cells in the blood should be expected. It is, therefore, interesting to compare studies of vein invasion and blood tumor cell isolation from regional veins: lung, 71% and 78%; stomach, 57% and 53%; and colorectal region, 33% and 30%.

Data on Tumor Cells

Survival.—Probably 99.9% of all tumor cells released into the blood stream fail to survive and establish metastases, since few patients with advanced malignancy have a systemic distribution of miliary metastases. The number of tumor cells released into the blood stream daily from a large primary or metastatic growth probably ranges from hundreds to thousands.

Roberts and co-workers [4] recorded the disappearance of tumor cells from the blood coincident with surgical excision of a circumscribed lesion. We have also noted a decrease in tumor cells in the peripheral blood after cancer chemotherapy. Unfortunately, most of the drugs are relatively ineffective against the solid tumors, and in a few days or weeks cancer cells again appear in the blood.

The prognostic significance of finding tumor cells in tumor veins and in the peripheral blood vessels is unsettled. Engell [9] has claimed that the five-year survival of patients with tumor cells in blood samples from veins directly draining the tumor sites was the same as that of a comparable group of patients with negative findings. A preliminary follow-up of our patients indicates a longer survival of patients with tumor cells in the blood.

Tumor Cells in Marrow.—The finding of tumor cells in the marrow was first reported in 1935. In 1958, we described a series of 305 cases in which both peripheral blood samples and sternal marrow aspirations were examined for the presence of tumor cells. Surprisingly, the frequency of abnormal cells was about the same (8%) in both marrow and blood.

Tumor Cells in the Lymphatics.—The monograph by Willis [10] is an excellent source of information on the subject of tumor-cell spread in the lymphatic system. Our own studies are providing information as to the number of tumor cells released into the blood from the lymphatics. Of lymph samples obtained from the cisterna chyli during postmortem examinations, 16% contained tumor cells. In addition, the thoracic duct has been cannulated in 50 patients with advanced disease. In 11 patients (22%), tumor cells were recovered. Tumor cell levels in the draining lymph were sharply reduced after the institution of chemotherapy, even if the primary tumor did not regress in size.

Tumor Cells in the Body Cavities.—Cancer cells also exfoliate into the spinal fluid, pleural cavity, and abdominal cavity. The frequency of this phenomenon varies greatly according to the kind of tumor. For example, over 95% of all deaths from ovarian cancer are associated with carcinomatosis of the peritoneal cavity.

In this clinic, routine washes of the peritoneal and pleural cavities are accomplished by spraying the viscera with 20 ml. of saline and recovering the fluid from the cul-de-sac. The fluid is centrifuged, and smear preparations of the cells are made. Washings are done both before and at the end of the surgical procedure. About one-third of all patients with curable intra-abdominal malignancy and two-thirds of those with noncurable lesions had positive washings. Even limited malignancies of the ovary were frequently associated with tumor cells in the peritoneal cavity.

These studies indicate that despite adequate surgical excision of many malignancies, cancer cells undoubtedly remain in the body cavities and may constitute an important source of recurrence. The importance of such findings is related to the proposed use of chemotherapeutic agents in body cavities as an adjunct to excisional surgery.

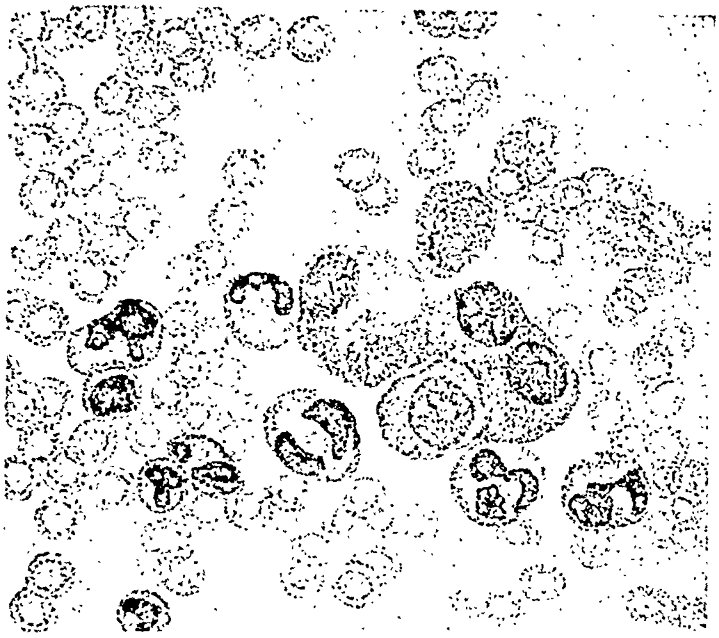
Factors in Spread of Tumor Cells

Role of Physician.—Studies of the transplantation and spread of cancer cells by biopsies and other surgical procedures have resulted in many interesting publications. The various kinds of iatrogenic spread of malignant cells are as follows: (1) careless, rough manipulation of malignant masses; (2) incomplete excisional, incisional, and needle biopsies; (3) direct contamination of surgical gloves and instruments with cancer cells; (4) indirect tumor cell contamination by means of the wash water used for packs and instruments; (5) rupture of malignant cysts; and (6) transection and subsequent suture of an intestinal lumen contaminated with tumor cells. Avoidance of undue manipulation; the use of separate drapes, instruments, and gloves for biopsies; the addition of anticancer agents to wash water; careful isolation of the tumor-containing segment of bowel—these and similar preventive measures should be routine.

Role of Surgical Wounds.—Spread of cancer cells in surgical wounds is a topic that has received much attention, and there are many reports in the literature attesting to its occurrence.[11] Surgeons have recommended washing the surgical wound with copious amounts of saline, dilute antiseptics, and distilled water. Experimental studies indicate that the compounds most effective for the local destruction of tumor cells are nitrogen mustard, actinomycin D, Dakin's solution, and other compounds which have not been evaluated completely in either animals or man. Although these compounds will destroy tumor cells in concentrations which do not impair wound healing, the adverse effects of high concentrations of these toxic compounds have been therapy, knowledge of various modes and routes of tumor cell spread assumed practical importance, for the increased *susceptibility of nonestablished* tumor cells in the blood, peritoneal cavity, and surgical wounds to carcinostatic agents had been demonstrated by laboratory experiments.

Spread of Tumor Cells in the Blood Stream

Engell[2] found that 50% of patients with advanced cancer had malignant cells in the peripheral blood. In addition, he studied blood samples removed from veins directly draining primary tumor sites. Positive blood specimens were found in 75% of patients with lung cancer and 59% of 107 patients with colorectal cancer.



Several large cancer cells isolated from blood sample removed from pulmonary vein during surgical excision of bronchiogenic carcinoma. Concentrated blood smear shows relative size and appearance of tumor cells in contrast to normal regular elements.

Our group[3] has used a fibrinogen-heparin solution to obtain rapid sedimentation of red blood cells. The plasma is drawn off and centrifuged, and smears of the buffy coat are stained with Wright-Giemsa stain. In a preliminary series of 179 patients with advanced cancer, one-half of the peripheral blood samples contained tumor cells. The frequency of finding tumor cells in the blood varied not only with the stage of the disease but also with the kind of tumor. For example, the regional blood samples were positive in 78% of the patients with lung cancer, in 53% of those with gastric tumors, and in 30% of those with colorectal lesions. In a subsequent series of 44 patients with colorectal cancer, there were only 16% positive regional vein specimens from those with resectable lesions, as contrasted with 37% from those with nonresectable tumors. We noted a greater frequency of tumor cell clumps in the blood of veins draining tumor sites than in samples obtained from the peripheral blood. It is interesting to speculate whether there would be a greater chance of such clumps being able to establish metastases.

Roberts and co-workers[4] performed parallel studies. Tumor cells were found in the peripheral blood of 17% of the curable patients and 28% of those deemed incurable. The blood of patients with cervical carcinoma was examined specifically for tumor cells by Diddle and co-workers.[5] No tumor cells were found in peripheral blood samples, but 8 of 14 aliquots of blood from regional veins were positive. A similar technique was used by Seal.[6]

Malmgren and his colleagues[6A] devised still another tumor-cell isolation procedure. Streptolysin O was used to destroy both the erythrocytes and a majority of the neutrophils, and the tumor cells were trapped by filtering the plasma through a millipore filter. Excellent tumor-cell recovery rates and high accuracy have been reported. Morley[7] found tumor cells and cell clumps in blood samples drawn from the superior sagittal sinus of two patients with brain tumors. This is particularly interesting, since metastases from such tumors are extremely rare—if they occur at all.

Mention should be made of the recovery of nonmalignant cells from the blood. For example, endothelial cells, macrophages, and even epithelial cells may be seen, particularly after surgery. Douglas and co-workers[8] found trophoblastic cells in veins draining the uterus during pregnancy; none were found in the peripheral blood.

The circulation of tumor cells in the blood stream and their ultimate fate are both interesting and important. The known physical factors include the size of the tumor cells and their deformation, the size of tumor cell clumps, the relative functional diameter of the capillaries in various organs, and the existence of arterial-venous and venous-venous shunts.

We have measured the size of both tumor cells and tumor cell clumps after fixation and staining by the Wright-Giemsa method. The average diameter of tumor cells in the peripheral blood was 19 μ (neutrophils had an average diameter of 11.7 μ), and they ranged in size from less than 10 up to 36 μ. Cancer cell clumps had diameters ranging from 15 (2 cells) to 110 μ (40 cells) (see figure).

It must be remembered that measured diameters of fixed cells are not synonymous with their physiological diameters. In attempts to screen out the larger tumor cells from normal cells, it was found that tumor cells would deform and pass through apertures of less than 10 μ. Similar observations have been made on growing tumor cells in Algire chambers.[8A] A tentative conclusion is that some tumor cells can probably pass through capillary beds as well as through various blood vessel shunts both in and around organs.

ination, diagnostic procedures, and operative manipulations. Tumor cells can be isolated from the peripheral blood of patients with malignancy and from the veins draining the primary tumor. In a few instances, cancer cells have been found in the blood of patients with small, curable lesions. The frequency with which tumor cells of different kinds of malignancies are found in the blood parallels histological observations of blood-vessel invasion. Tumor-cell invasion of the marrow is detectable if clumps of cells or growing metastases are present.

Examinations of washings of the body cavities have disclosed that cancer cells commonly exfoliate. Positive washings were more frequent in patients with ovarian carcinoma. Experimental models of clinical observations are useful but not directly pertinent to malignancy in human beings. Nevertheless, these observations aid in understanding the mechanisms of the establishment of metastases.

The study of tumor-cell dissemination is particularly worthy of attention because of the great number of chemotherapeutic, radioactive, and immunological agents being found which may have clinical value. Some anticancer agents probably will be useful clinically against unestablished tumor cells, even though they are ineffective systemically against solid tumors.

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THE ACTION OF ADRENOCORTICAL STEROIDS.—There have emerged two basic principles which should underlie the use of adrenocortical steroids. First, these agents are suppressive rather than curative. Second, their use involves the induction to some degree of a hyperadrenocortical state. Numerous studies have failed to establish a deficiency or imbalance of adrenocortical secretion or corticotropin activity as characteristic of any of the rheumatic diseases. Therefore, the use of these agents cannot be considered in any sense as substitution therapy. In their clinical use the dramatic suppressive effect is on the acute inflammatory manifestations, particularly those which may be attributed to the exudative phase of inflammation. With continued observation it is apparent that the chronic proliferative phase of inflammation, as for example the granulomatous destruction of cartilage in rheumatoid arthritis, may progress slowly over a period of months or years in spite of the almost complete suppression of the more acute inflammatory features by these agents.—W. D. Robinson, M.D., The Use of Adrenocortical Steroids in Diseases of Connective Tissue, *The University of Michigan Medical Bulletin*, October, 1959.

demonstrated. Nevertheless, general toxic reactions are appreciably less when chemotherapeutic agents are used in surgical wounds and in the body cavities than when they are given systemically. It would seem that these applications of the chemotherapeutic agents will be immediately useful against some tumors.

The recurrence of cancerous growth of the bowel at the suture site from tumor cells exfoliated into the lumen has been described by Cole and colleagues.[12] A separate series of chemotherapeutic agents is being sought for prophylactic treatment of the intestinal tract. Clinical use of these chemical adjuvants requires further careful study. We do not recommend their routine use at this time.

Fate of Exfoliated Tumor Cells.—As previously mentioned, there seems little doubt that most tumor cells released from the primary tumor are promptly destroyed. Even patients with advanced tumors have a relatively small number of metastases in comparison with the number of malignant cells which can be recovered from the blood and lymph. An occasional patient with malignant melanoma may demonstrate the potential situation which would be found if the majority of exfoliated tumor cells were capable of sustained growth. Such patients may have literally thousands of individual metastases in all tissues of the body. In contrast, volunteer patients with advanced disease cannot be successfully reimplanted with their own tumors, in most instances.[13] Certainly these evidences of host resistance require further study.

Future Studies.—In future years it should be possible to assess more accurately the spread of cancer cells. The techniques for such studies include accurate cytological examinations of the cells in lymph, blood, and marrow, with the aid of fluorescent microscopy, radioisotopically tagged cells, fluorescent antibodies specific for individual tumors, and quantitative assays of the number and viability of cancer cells by tissue culture.[14]

Practical Aspects

In the last several years, many new cancer chemotherapeutic compounds have been found. The National Cancer Chemotherapy Service Center alone tests more than 40,000 compounds each year for anticancer activity. Of the compounds which successfully pass animal-tumor screening and pharmacological studies and are introduced into initial clinical trials, most will probably be ineffective or too toxic for systemic therapy. Some may be clinically useful for local therapy against tumor cells contaminating the body cavities or surgical wounds or, perhaps, as adjuvants to excisional therapy.

Furthermore, not all compounds are equally effective against different kinds of tumors, individual tumors of the same type, or even all metastases of a single tumor. Much work will be necessary to assess the effectiveness of each compound against each kind of tumor cell. For example, we need in vitro tests of anticancer activity similar to those used for determining bacterial sensitivity to antibiotics.[15]

The successful application of the proper anticancer agent will depend on balancing its cytotoxic activity in malignant tissue against coincident injury to host factors. There is experimental evidence that toxic compounds may indirectly accelerate tumor growth by inhibiting normal defense mechanisms.[16] Clinical experience, as well as laboratory experiments, indicates that toxic chemotherapeutic agents which are relatively ineffective in destroying a malignant lesion may lower host resistance so that the net result is an actual acceleration of tumor growth. Until the results of systematic, valid studies of the values and limitations of these compounds against the solid tumors are available, they should not be used except in purposeful studies.

For all these reasons the study of the tumor cell spread deserves attention. Morphologic and anatomic studies should be supplemented by physiological studies. The mechanisms of the disassociation of cancer cells, tissue pressures, and cell motility must be determined. We should learn more about the adhesion of tumor cells to blood vessel walls, the role of fibrin as a protector of the cells from toxic substances, and how tumor cells penetrate into the tissues. Also, there seems to be reasonable evidence that conditions in various tissues differ in the support they afford tumor cell proliferation; perhaps "natural inhibitors" could be identified from such studies.

Comparisons of malignancy and the infectious diseases are trite. Nevertheless, as stated previously,[15] the evolution of the therapy of osteomyelitis provides a frame of reference for present attempts to use a combination of cancer chemotherapy and excisional surgery. Some years ago, chronic osteomyelitis was a relatively common disease. It was treated by expectant medical care, surgical drainage, and débridement. With the advent of the first partially effective sulfonamides, the combination of such drugs and less radical surgery was more successful. Now, with the preventive and early use of effective antibiotics, chronic osteomyelitis as a surgical problem has practically disappeared; rarely is extensive surgery necessary. Finally, it is interesting to note that, in those instances in which drug resistance has occurred, attempts are being made to bolster host resistance by providing "hyperimmunity."

Summary

Tumor cells disseminate through lymphatics and blood vessels, along organ lumens, and by exfoliation into the body cavities. Tumor cells may also be spread by the physician and surgeon during exam-

reacting threshold. Attacks end after all reacting bodies have united with specific food allergens. Thus, between attacks allergenic foods cause no symptoms. Regular reaccumulation above the reacting threshold explains the recurrent symptoms. If all reacting bodies are not exhausted, slight interim symptoms occur. Decrease or absence of attacks in the summer is best explained by increased solar radiation. Our experience also indicates that recurrent "head or bronchial colds" from fall to late spring are often equivalents of asthma due to food allergy rather than of infection.

When food allergy alone is responsible and is adequately controlled, true respiratory infections develop without resultant asthma. This supports our conclusion of many years that infectant allergy is a rare cause. Thus routine administration of antibiotics and chemotherapy is not indicated unless demonstrated secondary infection, especially in the lungs or tonsils, exists, especially after the second day of the attack. Symptoms of asthma itself require relief with therapy discussed later in this article.

Recurrence of bronchiolitis requires the consideration of inhalant and especially of food allergy as the cause. Adequate antiallergic control usually makes administration of corticosteroids unnecessary. If secondary infection occurs, antibiotic therapy is indicated. Wheezing, coughing, and dyspnea in patients with possible or evident cardiac impairment is often relieved by the control of unrecognized allergy, especially to foods.

When food allergy is the demonstrated cause, subsequent attacks are nearly always due to lapses in diet or to the addition of suspected or previously determined allergenic foods to determine possible tolerance as a result of their elimination. For such asthma, therapy with drugs, including corticosteroids, will give relief.

A similar or modified history of bronchial asthma due to food allergy occurs in adults and in older persons. Although recurrent attacks occur, with interim relief, recurrently exaggerated daily symptoms are usual. The role of food allergy in older persons [2] is shown in the following case report and in others in this article.

A woman aged 70 years had had recurrent attacks of bronchial asthma, exaggerated in the late fall and winter, for 14 years. No previous illness had occurred. Her mother had had indigestion from eating egg. A sister developed bronchial asthma at 64 years of age. The patient disliked drinking milk, and eating egg caused nausea and cough. The patient had had intractable asthma recently requiring fluid and electrolyte replacement and administration of corticosteroids. Physical examination, roentgenography, and laboratory studies revealed no evidence of other diseases. Results of scratch tests gave one-plus to two-plus reactions to pollens, with no reaction to foods. With our cereal-free elimination diet, asthmatic symptoms decreased in five days and were absent without use of steroid therapy in two weeks. Her asthmatic symptoms have been absent with a strict milk, egg, corn, and wheat-free diet and without use of medicaments.

In addition to recurrent attacks, severe symptoms may arise irregularly from infrequently eaten foods. When such allergy causes immediate bronchial asthma, large scratch reactions to the causative foods may occur. Thus, a woman aged 56 years had recurrent asthma in the fall and winter for eight years until she was 38 years of age. It had recurred for two months in the fall of 1957, being severe three times after the patient had eaten Chinese food. Skin tests were slightly positive to milk and eggs and extremely positive to soy beans. This indicated allergy to soy beans as the cause of the *severe immediate asthma. Such large reactions* justify routine testing with foods. With the control of other food allergies and house dust allergy, her daily asthma also disappeared.

Skin testing is highly fallible.[4] As we have long emphasized, most chronic cumulative food allergy is not indicated by positive results of skin scratch tests. Intradermal testing with foods is not done in our patients because of indefinite and false as well as negative reactions. Deaths from intradermal testing must be remembered. When the immediate symptoms arise from aningested food, a large scratch reaction often is obtained. Confirmation of allergy to a reacting food, however, requires occurrence of asthma after its ingestion by the symptom-free patient.

A dietary history of dislikes or disagreements [5] for specific foods should be routine. A positive history suggests possible food allergy. Many foods productive of clinical allergy, however, are not apparent to patients. Questions must be specific, as follows: Do you drink milk? If not, why not? Do you like eggs? Such questions about all ingested foods are important. Allergy to many foods, especially in unusual recipes, evades such questioning.

Diet diaries have rarely helped in determining all allergenic foods, especially condiments and ingredients in salads, desserts or cakes, or meals eaten away from home. Moreover, they are tedious for the patient and difficult for the doctor to interpret. When our elimination diets are prescribed, the time spent in reading diet diaries can be better used in being certain that the diet is strictly adhered to, that traces of allergenic foods are not being ingested, that bakery products are being properly prepared, and that nutrition and satisfactory weight are maintained.

Test Negative Diets

Because of the fallibility of skin testing in food allergy,[6] a diet excluding skin-reacting foods has infrequently controlled symptoms of bronchial asthma in our experience. Occasionally, the exclu-

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BRONCHIAL ASTHMA—ITS TREATMENT AND CONTROL

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The treatment of bronchial asthma necessitates immediate control of such probable food, inhalant, or drug allergies as might be indicated by the preliminary history. Food allergy, especially in children, is indicated by the pathognomonic history of cyclic attacks decreased or absent in the summer. Because of the fallibility of the skin test, especially in food allergy, test-negative diets usually fail to relieve asthma due to this cause. If food allergy is suspected, immediate ordering of cereal-free elimination diet is nearly always advisable. This diet should not be delayed until the skin testing is finished. Concurrent with control of specific allergies, the use of drugs, corticoids, ACTH, and indicated fluids and electrolytes to control severe or moderate symptoms, is imperative. These principles are exemplified in the histories of 10 patients.

Bronchial asthma has two important characteristics. First is the history of wheezing, dyspnea, heaviness or tightness in the chest, and coughing in recurrent or exaggerated attacks, with or without interim relief, often absent in different seasons. Second is the varying combination of physical findings, including wheezing with prolongation of expiration, rhonchi, rales, and evidence of obstructive emphysema.

Nonallergic causes[1] must be excluded by physical examination, laboratory, and x-ray studies. One should also be careful not to overlook acute and chronic laryngeal, tracheal, and pulmonary infections, new growths, foreign bodies, cardiovascular disease, hyperventilation, and other causes noted in the literature.

Although these alone may be responsible, they occasionally complicate allergic bronchial asthma. These studies may also reveal other indications of allergic asthma such as obstructive emphysema, eosinophilia, bronchial casts, Curschmann's spirals in the sputum, and positive skin tests.

When allergic bronchial asthma is the probable diagnosis, it immediately becomes necessary to hypothesize and initiate control of probable or definite food, inhalant, occasional drug and, in our experience, rare infectant allergies.[2] Along with this, relief of symptoms is an immediate challenge, especially in patients with severe or intractable asthma. This must not, however, supplant concomitant orders for the indicated cereal-elimination diet or environmental control as indicated by the patient's history.

Study and Control of Food Allergy

A pathognomonic history of bronchial asthma[3] (due to food allergy), especially in children, has long been shown in our cases. Attacks usually begin in the 18th to the 24th month, although they may commence at any time, including old age. They recur regularly every two to eight weeks. They are often absent in the summer, recurring from the fall to the late spring. Nasal allergy suggesting a cold often precedes and/or accompanies the asthma. Asthma with varying dyspnea, wheezing, tightness in the chest, or coughing then develops. This lasts for one to three days, with a sudden or gradual decrease up to five days. Anorexia may precede and continue during the attacks. When severe, vomiting and fever up to 104 F (40 C) due to food allergy and not to infection may occur. As the attacks recur, interim relief may be replaced by moderate wheezing, coughing, and tightness in the chest, especially with exercise and at night.

A girl aged 10 years developed asthma at 3 years of age. The asthma recurred from September to late spring at monthly intervals, with attacks initiated by "nasal colds," which were followed in a few hours by severe dyspnea, wheezing, fever, and at times vomiting. These decreased gradually in four to seven days, with no interim symptoms, and none in the summer. Previous treatment with test-negative diets and desensitization to dusts and inhalants had failed.

Results of skin tests revealed one-plus to two-plus reactions to several vegetables, fruits, and corn. With our cereal-free elimination diet, instead of a test-negative diet, symptoms of asthma were completely controlled. Later addition of other foods showed that milk and egg were the causative agents. Fruits, vegetables, and corn which gave skin reactions produced no symptoms.

These attacks are best explained by accumulation of assumed reacting bodies, in the cells of the nasobronchial tissues, to the allergenic foods above the

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someone in the physician's family or office must learn to prepare satisfactory bakery products with our recipes, in order that the physician can assure the patient that such products can be made at home. The physician may also find a baker who will make these products for sale, but only under the physician's supervision.

In the hospital it is easy to order the cereal-free elimination diet,[5] modified at times by diet history and by results of scratch tests. Nearly all dietitians have been instructed and have read about this and our other elimination diets and will cooperate with the physician in preparing them. The diet is written on the treatment page as follows: The cereal-free elimination diet, at times minus some foods or plus others to replace the eliminated ones, is ordered. If anorexia or nausea occurs the food can be ordered in a soft, puréed, minced, or semiliquid form. Calcium carbonate, one-half teaspoonful daily in water or food, or in capsules is indicated unless soy bean or meat base formulas containing calcium are taken. Multiple synthetic vitamins in drops or globules are necessary. Feedings of allowed foods between meals can be ordered. The physician must be sure the dietitian serves the diet accurately, with sufficient protein and calories, and must watch the trays and even taste the foods to determine their palatability. He must also be assured of weight maintenance.

Soybeans and other legumes at times disagree with or are found to be unpalatable by the patient. Muffins or hot cakes made from our recipes may be more acceptable than bread (see recipe). If these products are refused, then more white and sweet potato, tapioca, sugar, soybean or sesame seed oil, and the milk-free butter substitute along with other foods in the diet must be eaten to maintain nutrition and weight. The fact that foods remain in the body up to two weeks or longer emphasizes the need for absolute adherence to the diet. Thus, the usual recurrent attack or exaggeration of symptoms of asthma, especially in children, may occur in one week, a moderate one in two weeks, and at times a slight one in three to four weeks after the diet is started, even though the elimination diet excludes all foods responsible for the asthma. The next expected attack in two to six weeks, however, should be absent if all allergenic foods are eliminated from the diet. Errors in the diet or allergenic foods added after relief reactivate asthma.

Thus bronchial asthma which had been present for six years in a 67-year-old man was entirely relieved with the cereal-free elimination diet in one month. After two months of freedom from symptoms, addition of rice caused a recurrence of asthma within three days. Although rice was eliminated from the diet immediately, the asthma did not entirely disappear for three weeks. In some patients food allergens apparently do leave the body within a few days, as in a 55-year-old woman who had had perennial, nearly continuous, recurrently exaggerated severe asthma for 50 years. With the cereal-free elimination diet symptoms of asthma were less evident within three days and were absent within seven days. Symptoms have been entirely absent during the past two years, except on two occasions when slight lapses in the diet occurred. She is still unable to eat any cereal grains, wheat, eggs, chocolate, or spices.

Inhalation of odors of a food may prolong or cause asthma. This varies with the degree of allergy to the food. Bronchial asthma due to food allergy often improves or disappears in the summer and increases during the autumn, winter, and early spring.[8] Many patients require the elimination diet from autumn until April or May and can tolerate other or even all foods during the summer. Bronchial asthma due to food allergy may also decrease or disappear when the patient is away from the ocean.[8] This accounts, in our opinion, for the relief of much bronchial asthma in inland and usually dry areas, as in central and southern California and in the Rocky Mountains and southwest areas. With the proper cereal-free elimination diet such asthma is usually controlled in any area. This assumes that inhalant allergy, when associated with food allergy, has been studied and treated. So-called parentectomy rarely is necessary when food allergy is studied, according to our experience, and when inhalant allergy, if present, is adequately controlled.

If attacks, especially in children, have recurred every 2, 4, or 6 weeks,[5] absence of attacks must continue for 4, 8, or 12 weeks or longer before previously eliminated foods can be added. Relief of interim symptoms or of more constant asthma, especially in the autumn, winter, and early spring also occurs in two to six weeks with the elimination diet alone. When relief is assured, one food can be added daily for two to four days, beginning with fruits and vegetables not in the diet; later pork, fish, rice, oats, rye, and corn can be added. We usually postpone adding wheat, egg, and milk for three or more months. With such elimination of allergenic foods, especially during the middle of autumn to late spring, tolerance often develops in one year to three years so that a general diet or the sole elimination of one to three or more foods only is required. This increased tolerance occurs infrequently in adults as compared to children. When foods are added and tolerated during the spring and summer, they may cause bronchial or nasal allergy in the autumn and winter, again necessitating use of the cereal-free elimination diet. Thus a winter and summer diet may be required in some patients for several years.

If some relief is not evident in two weeks, errors or allergy to foods in the diet may be the cause. The latter may not be suggested by history or positive skin tests. Before ruling out food allergy, beef (which contains a globulin also present in milk), sion of foods to which extensive reactions occur and/or those which are disliked by or disagree with the patient relieves symptoms of asthma. If asthma is not controlled thereby, food allergy cannot be ruled out without a trial diet, for which we advise our cereal-free elimination diet in patients with bronchial asthma. Indeed, we nearly always use this diet rather than one excluding reacting foods.

The Cereal-free Elimination Diet

Our recognition, for 30 years, of food allergy in bronchial asthma has largely depended on the use of our cereal-free elimination diet.[5] In contrast, a diet eliminating foods suspected through diet history or by large scratch reactions infrequently gives relief. Our work continues to reveal food allergy as a sole cause in about 20 to 40% of patients with bronchial asthma, especially in children, and in association with inhalant allergy in 30 to 50%.[7] Since our diet is used whenever food allergy is suspected, its use does not a priori imply food allergy. However, with its accurate use we are assured that this frequency of food allergy will be confirmed.

This cereal-free diet should be ordered when the patient is first seen, if the classic history of bronchial asthma due to food allergy or its modifications is obtained. Moreover, it should be used to study food allergy in practically all patients with perennial bronchial asthma even though inhalant allergy is also indicated.

In office cases, the physician or his assistant must give the patient or parents a printed or typewritten list [5] of allowed foods, with menus and recipes for the soy-potato bakery products. It is mandatory that the patient eat no trace of any food not in the diet and maintain a desired weight. Moreover,

TABLE 1.—*Cereal-Free Elimination Diets*

Tapioca
White potato
Sweet potato or yam
Soy-potato bread
Lamb or beef[*]
Chicken (no hens)
Bacon
Lettuce
Spinach and chard
Carrots
Artichokes

Tomato and squash
Asparagus
Peas and stringbeans
Lima beans
Lemon and grapefruit
Pears and pineapple
Peaches
Apricots

Prunes
Cane sugar
Salt (noniodized)
Soy oil and Willow-Run[†]
Gelatin, plain
Maple or cane sugar syrup
White vinegar, *vanilla*
Cornstarch-free baking powder[‡]
Soy milk or water

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[*] Since beef allergy occurs in some persons with milk sensitizations, it can be eliminated initially or later if relief fails.

[†] Willow-Run butter substitute contains hydrogenated soy oil, butter flavor, and salt (Shedd-Barbush Foods, Inc., Detroit 38, Mich.).

[‡] Cornstarch-free baking powder, Chicago Dietetic Supply, Inc., 1750 W. Van Buren St., Chicago, or F. A. Bray, 3704 Piedmont Ave., Oakland, Calif.

Simplified Menus

Breakfast

Juice of fruits on diet or tomato juice
Tapioca cooked with fruit and sugar, or white or sweet potato (baked, boiled, or fried in allowed oils or fats)
Bacon and fried potatoes
Lamb or beef (chops, patties, steak, *roast*, *tongue* [unspiced], strained, or diced canned meats [Gerber's or Swift's]; bacon)
Soy-potato bread or muffins
Pancakes or waffles of soy flour and potato starch
Willow-Run or soy oil with salt as a butter substitute
Jam or jelly made from specified fruits
Fruits (fresh, cooked, or canned) on diet
Soy milk, in infants and children especially

Lunch or Dinner

Soup made with strained meat (*Gerber's* or *Swift's*) or broth (lamb *or beef*); no spices; no soups made away *from home*; no canned soups
Lima bean or split pea soup, plain, flavored with salt and bacon (not canned)
Salad of prescribed fruits or vegetables, fresh or cooked, with soy oil, lemon, white vinegar, salt and sugar
Meat as at breakfast (no pepper or condiments)
Vegetables on diet, plain, cooked with salt
White or *sweet* potato (baked, boiled, or fried in prescribed *oils or* Willow-Run)
Bread, butter substitute, jams and jellies (see breakfast)
Desserts: Fruits on diet, tapioca (see breakfast). Gelatin made with prescribed fruits and sugar (no Jello). Cake and cookies made of soy flour and potato starch; candy *made* at *home* of prescribed foods on diet; maple sugar

Cereal-Free Elimination Diet for Infants

Soy bean milk or strained meat formula (Gerber's)
Multiple liquid synthetic vitamins, 5 drops daily

Other foods in the cereal-free elimination diet can be added according to the infant's age, desire, digestion, and allergic tolerance. Strained cooked canned vegetables, fruits, and strained (in older infants, ground) meats are given.

Comment: More detailed menus with additional recipes and directions for the preparation and use of these diets are published elsewhere.[6]

Elimination of canned fruits, peas, drinks, and other foods such as some bacon containing dextrose may be necessary to control corn allergy.

Absolute adherence to the diet is imperative. If undesirable weight loss occurs, more of the prescribed carbohydrates, *sugar, fats, and oils must be taken.*

Soy-Potato Bread, Muffins, or Pancakes[*]

1 cup soy flour
1 cup potato starch flour
1 tsp. salt
¼ *cup soy oil*
3 tbsp. baking powder
2 tbsp. white sugar
1⅛ cups water

Measure flours lightly to 1 cup level in *measuring* cup. Sift *dry ingredients* once. Add water and beat 3 minutes. Add *oil and* beat *1 minute* longer. Grease baking pan well with soy oil. Preheat oven to 350 F. Bake at 350 F for 10 minutes. Reduce heat to 285 or 300 F and continue baking *for 1 hr. 20 min.*

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[*] Bake muffins at 300-325 F for 25 to 30 min. Makes 12 muffins. For pancakes or waffles thin this batter with ¼ cup of water.

NOTE: Other recipes may be found in other publications.[6]

When their inhalation is unavoidable, desensitization is justified by the good results obtained by many allergists.

Allergy to house dust too often is assumed from definite skin reactions which may be nonspecific. Many cases of asthma with reactions to house dust have been relieved with our cereal-free elimination diet alone or combined with desensitization to pollens and none to dusts. This also applies to the perennial nasal allergy in which food allergy too frequently is entirely unsuspected.

Briefly, desensitization with inhalants requires a gradual increase in the strength of the antigens without exaggeration of symptoms. In our experience, initial dilutions usually vary between 1:50,000 and 1:1 billion or weaker, as determined by serial intradermal titration and especially by their clinical effects. If overdosage is suspected, discontinuation of injections for three to four weeks may be advisable.

Smoke from tobacco, wood, sulfur, and other sources and fumes of paints, varnishes, petroleum products, waxes, and other chemicals often increase or activate symptoms of bronchial asthma. When causative food or inhalant allergies, or both, are controlled, these effects may disappear. Allergies to petroleum products, natural and synthetic rubber, plastics, and other chemicals do exist. According to Randolph,[9A] petrochemical allergies explain some poor results of treatment of chronic bronchial asthma and other manifestations of clinical allergy. Reports of his studies and of other students of such hypersensitivity deserve definite consideration.

The association of food with inhalant allergy too often is overlooked. This is due to failure to study food allergy because of negative skin reactions, to the use of test-negative diets which nearly always fail to relieve food allergy, and to failure to use the cereal-free elimination diet as we have long advised. Moreover, failure often results from desensitization given for months or years for assumed allergy to inhalants only on the basis of positive skin reactions, when food allergy is entirely responsible. This is illustrated in the following case.

A 32-year-old woman had had perennial bronchial asthma for 25 years, especially in the autumn to late spring. For 12 years she had been constantly desensitized to various inhalants with no benefit. In one month after the cereal-free elimination diet was started and desensitization to inhalants had been stopped, her asthma was entirely relieved, and has continued to be for three years except briefly after lapses in use of the diet.

Food allergy can develop in patients whose symptoms were previously controlled with use of pollen therapy. Thus, symptoms of hay fever and moderate asthma in the spring and fall in a 34-year-old man were controlled by perennial pollen therapy for two years. For two years, however, asthmatic symptoms had increased in the late autumn and winter. Since the patient worked in a nursery, occupational inhalants, including additional pollens, were suspected. Failure to achieve relief justified study of food allergy. With our cereal-free elimination diet, improvement in two weeks and excellent relief after one month resulted and has persisted with the proper diet. Pollen desensitization has been continued.

The exacerbation of this patient's asthma in the winter in spite of negative skin reactions to food justified study of food allergy with the use of our cereal-free elimination diet. The onset of food allergy in a patient with asthma previously controlled with pollen therapy is illustrated.

When food allergy and inhalant allergy are suspected in patients with bronchial asthma, possible allergic bronchitis, bronchiolitis, or perennial nasal allergy, the cereal-free elimination diet should be prescribed for at least three weeks. In infants this diet is modified according to age.[5] If definite relief occurs, the diet is continued, and inhalant allergy is ignored. If no relief occurs further study of possible food allergy usually is advisable, and study and possible control of inhalant allergy is begun. Such treatment of inhalant allergy is justified by a history of probable or definite allergy to inhalants, and not by positive skin reactions alone. In fact, negative skin reactions to inhalants causing bronchial asthma occur in 10 to 15% of patients. With this plan, much prolonged desensitization with inhalants has been stopped or obviated. Such cases, especially in children but also in adults and elderly persons, controlled with the cereal-free elimination diet alone and with no injections of antigens or vaccine, have been reported in an article on bronchial asthma due to food allergy alone.[3]

Infectant Allergy

Our experience for 40 years emphasizes the infrequency of infectant allergy as a cause of bronchial or nasal allergy.[10] It contradicts the conclusion that infections cause initial symptoms or colds and associated or subsequent bronchial asthma, with or without fever, especially in children. It also refutes the opinion of many allergists that infectant allergy causes much asthma in adults and old age, especially in the fall and winter. With the control of inhalant and especially food allergy, infectious colds occur with no resultant asthma. Moreover, the control of bronchial asthma has rarely, if ever, resulted from stock or autogenous vaccines alone. Asthma has been relieved, in a rare patient, by removal of definitely infected tonsils or teeth, although asthma arising after tonsillectomy has long been reported.[1] Increased resistance to respiratory infections may also arise, from increased immunity or nonspecific effects from vaccine therapy.

This lack of evidence of bacterial allergy [10a] does not exclude possible activation or increase of bronchial asthma from acute or chronic bronchial in-legumes, or at times some or all fruits, and less often vegetables, should be suspected. Indeed, *initial elimination of beef from the diet is justified when allergy to milk is probable.* In our experience allergy to white potato is infrequent. Thus, recurrent asthma of six years' duration in a woman aged 27 years, finally producing constant asthma, was not relieved in two months by our cereal-free elimination diet. Desensitization on the basis of slight reactions to pollens, animal emanations, and house dust likewise was ineffectual. Prednisone, 10 to 15 mg., taken for one year, also failed. Then beef, and later all fruits, was eliminated from the cereal-free elimination diet with relief in 10 days, being complete in three weeks. This relief has persisted with the continued elimination of all cereals, all fruits, beef, and milk.

It is our conviction that physicians usually fail to recognize most of the food allergy in bronchial asthma unless the cereal-free elimination diet is properly used, as we have long advised. *It is as necessary to suspect all cereals as it is milk or egg.* This holds for persons in old age [2c] as well as for those in younger years. The technique of the use of the diet and its indicated modifications, the errors that often occur, the necessary maintenance of desirable weight and nutrition, and the philosophy toward the necessary strict and often prolonged elimination of allergenic foods have long been published.[8A] They should be known to all physicians who assume the study and control of bronchial asthma.

In patients with perennial asthma, not limited to pollen seasons, or not arising from some other inhalants, the study of food allergy with this diet should be routine. A woman aged 26 years had bronchial asthma from the autumn to the spring months for six years. Severe symptoms had developed in November after the birth of her last child, causing constant bronchial asthma for 11 months before we saw her. In April, resection of her lower left lung was performed because of apparent bronchiectasis. Decortication to remove a membrane over the lung, due to infection with Bacillus proteus, was also performed. Symptoms of asthma continued before and after these operations. Her history suggested possible food allergy. Skin reactions to foods, however, were negative. With the cereal-free elimination diet, and administration of 30 mg. of prednisone, marked relief occurred in seven days. Asthma disappeared and administration of prednisone and other medicaments was stopped in one month. Asthma has been absent for two years. Cereal grains, milk, and egg *still* reactivate her asthma.

In our opinion, this asthma could have been controlled six years previously, and the lobectomy and subsequent decortication would have been obviated if the cereal-free elimination diet had been used.

We continue to relieve adults and older persons of bronchial asthma even of lifelong duration, with the control of food allergy, refuting the opinion that food allergy rarely or never occurs after the age of 40 years.

A woman aged 61 years had had bronchial asthma for 15 years, at first confined to the autumn, winter, and early spring months,[8] which had kept her in bed most of the winters. During the last 10 years in California, asthma had been continuous, still exaggerated in the winter. She had had two to four attacks every night, often awakening with marked dyspnea, choking, and near exhaustion, with mucus clogging her throat. She had had frequent colds with coughing through high school and college. Diet history revealed no suspected foods. Skin testing gave one-plus and two-plus reactions to feathers, wool, and several spring pollens.

With our cereal-free elimination diet she was markedly relieved in one week, with steady improvement during the next month. She slept all night, was relaxed, free of tension, and felt "100% better." The continued elimination of wheat and milk from her diet was necessary. No desensitization to the skin-reacting inhalants was given.

Etiology of Inhalant Allergies

A detailed history is the most important means of revealing suspected inhalant allergies. Asthma in the spring, summer, and autumn indicates pollen allergy. Airborne spores of fungi also should be considered. The history usually indicates asthma from animal emanations, house dust, feed, grain and other food dusts, and pyrethrum and other insecticides. Less often, inhalants as of cottonseed, castor bean, flaxseed, or fertilizers may be responsible.

Skin tests usually give positive results by the puncture or scratch method. The intradermal method is never used by us with cottonseed or flaxseed or with any other inhalants that give definite scratch reactions, because of possible fatal results. It must be remembered that many, even large, reactions to pollens and other inhalants may not be associated with clinical allergy. This was emphasized by complete relief with our elimination diet alone in 95 persons with bronchial asthma [3] in whom there was no desensitization to the skin-reacting inhalants. The clinical significance of reacting inhalants or of those which cause suspicion because of the patient's history depends on relief from environmental control and from gradual desensitization with those inhalants. Names of pollens causing allergy in all areas of the country are published.[9] In addition, a survey of the local trees, shrubs, flowers, and grasses in the patient's environment by the physician with the help of a botanist is desirable to prepare required antigens.

When allergy to animal emanations and house dusts is suggested by history or skin tests, or both, strict environmental control usually gives relief.

venously or 4 to 8 Gm. orally) should be given when large doses of corticosteroids or corticotropin are used.

Antibiotic therapy is always advisable to counteract secondary infection which may be masked by corticosteroid or corticotropin therapy. The choice of antibiotic should be governed by the resistance of the local hospital staphylococci. One antibiotic for possible gram negative and a second for gram positive organisms at first parenterally is necessary. This should be given before culture and sensitization studies are available.

Sedation of any type is initially contraindicated [5] because of its definite tendency to suppress conscious respiratory effort. Death may result. This applies especially to morphine, meperidine hydrochloride, and similar derivatives of opium. Narcotizing doses of codeine, barbiturates, and other sedatives are detrimental or even fatal in patients with status asthmaticus. Habit formation is also a constant danger.

Anoxia with resulting cyanosis is primarily the result of bronchospasm and mucous plugging. Oxygen should be administered only by mask or catheter but will be of little benefit until bronchospasm is relieved. Bronchodilators including epinephrine and isoproterenol hydrochloride may be given alone by nebulization or as aerosols with wetting agents. Positive pressure therapy is only occasionally beneficial and should not be used if it distresses the patient. Possible cardiac decompensation should be watched for. Right ventricular failure occurs most often. A large tender liver is the most reliable sign rather than cyanosis, venous distention, or edema. Its control requires digitalization.

If food allergy is suspected or known, the cereal-free elimination diet should be immediately offered in liquid, minced, or puréed form. As appetite improves, foods of regular consistency may be given.

If inhalant allergy is suspected or known, Dacron or foam-rubber pillows, a rubber or cotton mattress, cotton or synthetic blankets, and strict dust control should be used immediately. If pollen allergy seems probable, an adequate commercial or homemade filter [13] or air-conditioning device should be placed in the hospital or bedroom window. All types of inhalant allergy thereby are considered. Inhalant desensitization may be delayed for from one to four weeks. When status asthmaticus is relieved, the following medicaments and measures will suffice to control later severe and moderate asthma.

Severe Bronchial Asthma.—Severe bronchial asthma may be treated with epinephrine, 1:1,000, 0.20 to 0.80 cc., given hypodermically according to age every 2 to 12 hours. Administration of aminophylline, 3½ to 7½ grains intravenously (in adults) and later by suppository every 6 to 12 hours is advisable. Therapy with oral doses of 3 grains, one to four times daily, may be of help. Aminophylline therapy may be dangerous if the patient is under 7 years of age.

Administration of epinephrine, 1:1,000, or isoproterenol hydrochloride, 1:200, by inhalation may be beneficial. Five to 10 nebulizer bulb squeezes every 10 minutes for three occasions, and later every 1 to 12 hours may be increasingly beneficial.

Tablets or suspensions containing ephedrine and aminophylline with or without phenobarbital given orally in doses indicated by age may give relief. Isoproterenol hydrochloride given sublingually may be helpful. Therapy with racephedrine hydrochloride instead of ephedrine produces less nervousness.

Corticosteroids in doses of one to two tablets every two to eight hours, with subsequent reduction in dosage after relief, is justified. Small infrequent doses may result in therapeutic failure.

Therapy with potassium chloride, 1 to 4 Gm. a day, is indicated when more than one tablet of corticosteroid is administered daily. Adequate oral intake of fluids must assure hydration. Potassium iodide, saturated solution, 5 to 20 drops in water, three times daily, may be beneficial. Occasional iodide sensitivity must be watched for. This medicament, however, is used less frequently with the advent of newer drugs.

Immediate or continued use of the cereal-free elimination diet for possible food allergy and environmental control with subsequent desensitization with indicated inhalants is imperative.

Moderate Asthma.—Epinephrine, racephedrine hydrochloride, aminophylline therapy, or any combination of these, with or without phenobarbital may give relief. Use of epinephrine, 1:100, or isoproterenol hydrochloride, 1:200, by inhalation is also effective. Aminophylline suppositories in doses according to age may be of help in patients aged over 7 years.

Corticosteroids should not be given without persistent effort to control symptoms without them. Discontinuation of all medication is the physician's challenge. This can occur only with adequate control of existent food, inhalant, and infrequent drug and rare infectant allergies. Of these, we are assured that food allergy is too frequently overlooked or inadequately controlled for reasons [6] already stressed.

Administration of corticosteroids, other medicaments, and injections of inhalants could not be discontinued for three and one-half years in four children until asthma was controlled by our cereal-free elimination diet. In one boy the diet had been prescribed over a year before but had not been strictly adhered to, and some cereals were added before relief was assured.

fections when food or inhalant allergies, or both, are uncontrolled. Moreover, the importance of eliminating acute and chronic infections in the bronchial and other tissues of the body to improve general health along with the use of antibiotics and, if indicated, with chemotherapy is obvious.

Drugs can cause various allergic manifestations. Bronchial asthma, however, occurs infrequently in comparison with the cutaneous, joint, and gastrointestinal manifestations of allergy and allergic fever due to drugs. Many patients with chronic asthma develop severe asthma or even die from use of acetylsalicylic acid and animal serums. Alexander[11] has also listed reports of rare, usually moderate asthma from acacia, chlortetracycline (Aureomycin), diphenhydramine (Benadryl) hydrochloride, cocaine, dehydrocholic acid (Decholin), meperidine (Demerol) hydrochloride, digitalis, fennel, ipecac, liver extract, mercurials, pancreatin, papain, para-aminosalicylic acid, penicillin, podophyllin, pyromen, quinine, sesame seed, stramonium, sulfobromophthalein sodium, sulfacyanates, sulfonamides, malt extract (Taka-diastase), tannic acid, thiamine, tragacanth, viomycin sulfate, and more frequently from castor bean and gum. This occurrence of asthma from the above substances indicates its likelihood from others which have not been reported, or will be in the future.

Nonspecific Control of Symptoms of Bronchial Asthma

Thus far the importance of the immediate study of food, inhalant, and occasional drug allergies on first seeing the patient, and the continued study and control of such allergies aided by skin testing, environmental control, and indicated desensitization to inhalants has been emphasized. Concomitant with this initial study, symptoms must be controlled as rapidly as possible with drugs, corticosteroids, corticotropin, and other indicated therapy. The goal of all therapy in bronchial asthma, however, must be its control with antiallergic therapy alone, with little or no medication of any type.

Severe Intractable Asthma (Status Asthmaticus).–Severe intractable asthma (status asthmaticus) should be considered a serious medical emergency,[12] and is best treated in a hospital. Epinephrine, 1:1,000, 0.2 to 0.8 cc., should be given hypodermically according to age every 10 to 15 minutes. If after five injections there is little or no relief, the patient is temporarily epinephrine-fast. Wheezing, rales, and rhonchi are often suppressed by severe bronchospasm.

Aminophylline, 3¾ to 7½ grains (0.25 to 0.5 Gm.) in adults and 1½ to 3 grains (0.1 to 0.2 Gm.) in children, according to age and weight, given slowly intravenously (5 to 10 minutes) is often beneficial. The dose may be repeated every 6 to 12 hours. It may be incorporated in necessary intravenously given fluids or injected directly into the tubing. Overdosage may produce peripheral vascular collapse and even death. The most frequent toxic symptom is vomiting. Administration should be stopped at once if toxic symptoms appear.

Corticosteroids, intravenously or intramuscularly administered, should be given immediately. Adequate doses should be repeated every three to six hours until relief is apparent. Concomitant oral administration of one to two tablets of the chosen preparation (table 2) every two to three hours also is advisable. Dosage may be reduced gradually to one or two tablets four to five times daily after cessation of parenteral therapy. This dosage is indicated regardless of the patient's age and weight. Our experience indicates that therapeutic failures most frequently result from inadequate corticosteroid dosage. Tablets may be crushed and mixed with syrup of raspberry (one tablet per dram) for administration to infants, children, and adults who cannot swallow pills. Occasional corticosteroid sensitivity may develop.

TABLE 2.–*Medication in Treatment of Severe Intractable Asthma*

Drug	Dosage, Mg.
Orally Administered Corticosteroids*	
Cortisone acetate	25
Hydrocortisone	20
Prednisone (Deltra, Deltrasone, Meticortin)	5
Prednisolone (Cohydeltra, Meticortelone)	5
Methylprednisolone (Medrol)	4
Triamcinolone (Aristocort, Kenacort)	4
Dexamethasone (Decadron, Deronil, Gammacorten)	0.75
Parenterally Administered Corticosteroids†	
Cortisone acetate—aqueous suspension	100
Hydrocortisone sodium succinate (Solu-Cortef) (I.V. or I.M.)	100
Prednisolone sodium succinate (Meticortelone, soluble, Hydeltra)	50
Prednisolone butylacetate (*Hydeltra-T.B.A.*)	40
Corticotropin (ACTH) powder, 40-80 U. (I. M. or I. V.); gel, 40-80 U., I. M. only	

* *Maximum single tablet size.*
† *Maximum single dose.*

Corticotropin (ACTH), intramuscularly or intravenously given every four to six hours, may be effective. Because maximum adrenal cortical response occurs only after four to five days, benefits from such therapy are frequently delayed. For this reason and because of the prompt benefit obtained from corticosteroids, corticotropin is infrequently used. Species sensitivity may develop, necessitating a change in the preparation, or true organ sensitivity (pituitary) may occur, requiring complete cessation of corticotropin therapy.

Fluid and electrolyte therapy is important to correct dehydration and chemical disturbances. Fluid deficits are frequently large (3,000 to 7,000 cc. in adults), requiring replacement by both oral and parenteral routes. Serum sodium, chloride, carbon dioxide, potassium, and hematocrit determinations, along with sound clinical judgment, must guide such therapy. Potassium salts (20 to 60 mEq. intra-control of possible food, inhalant, or drug allergies relieves the initial and recurrent symptoms of bronchial asthma, their control with the aforementioned drugs and other therapy is necessary. Correction of dehydration and electrolyte deficiency, especially in patients with intractable asthma, is imperative. Nutritional and vitamin requirements must be satisfied.

Before corticoids were available our immediate and subsequent study for the control of food allergy and inhalant allergy alone, with relief of initial and subsequent symptoms with the above drugs, nearly always gave relief in a few days or weeks.[14] Although this initial control of food and inhalant allergy, with relief of symptoms, with former drugs still gradually controls most bronchial asthma, the conjunctive use of corticosteroids usually hastens relief in three to five days. As the elimination diet and the control of inhalant allergy become effective, the dosage of corticosteroids can be reduced and often eliminated in 3 to 20 days. Final dependence on antiallergic therapy alone without drugs or hormones must be the goal of the physician.

Summary

The treatment of bronchial asthma necessitates immediate control of probable food or inhalant and occasional drug allergies as indicated by preliminary initial history. Rare infectant allergies need later consideration.

Food allergy is indicated by the pathognomonic history of cyclic attacks decreased or absent in the summer, especially in children, and by a similar or equivalent history in adults and elderly persons. It is also indicated by perennial asthma, at times with cyclic exaggeration, and also by a history of food disagreements and dislikes.

Because of the fallibility of the skin test, especially in food allergy, test-negative diets usually fail to relieve asthma due to this cause. Thus, if food allergy is suspected, immediate ordering of our cereal-free elimination diet is nearly always advisable. This should not be delayed until the fallible skin testing is finished. Without the initial exclusion of cereals as well as of milk, egg, fish, nuts, and other foods, our control of symptoms of bronchial asthma due to foods would have decreased.

Inhalant allergy is usually indicated by the patient's history. Immediate environmental control is important. In pollen allergy, efficient homemade or commercial filters are valuable. Desensitization to those inhalants which cannot be eliminated from the patient's environment is important.

With this initial study and control of specific allergies, the immediate use of drugs, corticoids, ACTH, and indicated fluids and electrolytes to control severe or moderate symptoms is imperative. Practically all articles on the treatment of bronchial asthma are devoted nearly entirely to the indications and use of these medicaments, with inadequate or no attention to inhalant and especially to food allergy.

2940 Summit St. (9).

Case reports in this article are limited to patients with bronchial asthma due to food allergy alone or associated with inhalant allergy, because of the too-frequent failure to consider, recognize, or control this cause. Those due to the generally recognized inhalants alone are not included.

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A boy, aged 8, had perennial asthma, moderately better in the summer, for five years. Slight reactions only occurred to grass pollens. With the cereal-free diet given in January, 1953, symptoms of asthma rapidly disappeared for three months. Then pollen and dust desensitization was started, followed by the addition of egg and corn and later wheat to the diet. In June, symptoms of asthma recurred. In spite of continued desensitization, varying degrees of asthma persisted perennially for five years. Because of the initial control of asthma with the cereal-free diet, we advised its resumption in the fall, but the patient refused to cooperate. During the next five years, individual foods were excluded briefly with no help. Finally, more than three years ago, the strict cereal-free diet was resumed. After its use for three weeks, complete relief resulted. The dosages of cortisone, given for two years, and prednisone, for the next two years, gradually were reduced. No medicaments have been given for the last three years, except when ingestion of rice, oatmeal, wheat, or milk reactivated his asthma.

According to our experience and present opinion, the delay in controlling this perennial bronchial asthma and the use of corticosteroids for four years could have been prevented if strict and willing cooperation in the use of the cereal-free diet had continued after its initial benefit seven years ago. It is probable that the desensitization for four years was unnecessary.

Comment

Physicians must realize the necessity of the immediate study of evident or possible food, inhalant, or less frequent drug or chemical allergies when the patient is first seen. Food allergy especially needs initial study, as indicated by the pathognomonic history of asthma due to food allergy as summarized in this and previous articles,[7] or by a perennial history of bronchial asthma, usually absent or decreased in the summer months with exacerbation during the autumn to the late spring months, or by a diet history suggesting food allergy. This study of such possible food allergy with our cereal-free elimination diet, rather than a general diet, is immediately indicated.

An initial history, moreover, of exacerbation or limitation of symptoms in the pollen seasons or from animals, house, occupational, or recreational dusts justifies immediate strict environmental control, and at times adequate pollen or dust filters in the home or hospital.

The physician should not postpone these orders until skin testing has been done, or because of absent or misleading reactions which occur in the great majority of food-sensitive, and in many inhalant-sensitive, patients. When consideration of food or inhalant allergy is delayed until such testing is completed, extended by some physicians unnecessarily for 3 to even 20 sittings, relief from antiallergic control is unfortunately delayed, and the necessity of drugs and other therapy for the relief of symptoms is prolonged. In our practice puncture tests with 20 to 60 inhalant and food allergens in infants and young children, and with 100 to 200 in older children and adults are done in 15 to 60 minutes during the first one or two days. If the large reactions to scratch tests suggest allergy to foods which are in the initial elimination diet, they can be omitted or replaced by other infrequently allergenic foods. Desensitization to indicated pollens or other inhalants which cannot be eliminated from the patient's environment should be started in the early days of therapy, if food allergy is not the sole probable cause.

Our long-reported pathognomonic history of recurrent bronchial asthma due to food allergy, especially, should be recognized by members of the profession. This is important, since the diagnosis of food allergy infrequently can depend on skin reactions to causative foods. A diet history suggestive of food allergy, moreover, infrequently indicates all the allergenic foods. Thus, the occurrence of the classic history or its equivalent requires adequate study of food allergy, especially with our cereal-free elimination diet. Perennial bronchial asthma, moreover, varying intermittently in degree requires such study along with that of possible inhalant allergy. The value of this diet depends on our long recognition of the frequency of possible allergy to all cereals in bronchial asthma along with allergy to egg, milk, chocolate, and less often to other foods eliminated from this diet. Our emphasis on food allergy, however, does not minimize the approximately equal importance of allergy to inhalants, less often to drugs, and rarely to infectants.[7]

This recognition and control of inhalant and especially food allergy reduces the occurrence or assumption of bacterial or infectious allergy as a cause of bronchial asthma to a low minimum. It also minimizes the temptation to diagnose intrinsic asthma, or psychogenic causes, which ignores the responsible antigen-antibody reaction.

This emphasis on or even discussion of the adequate study of inhalant and especially food allergy unfortunately is lacking, or is inadequate, in practically all articles on the treatment of bronchial asthma. Such discussions overemphasize the use of various drugs, including epinephrine, aminophylline, antihistaminics, or corticosteroids, inhalant therapy, ACTH, other new proprietary drugs, and even lung surgery (lobectomies or lobotomies). The conclusion might be drawn that the control of bronchial asthma usually depends on the use of such drugs or on the commitment of the patient to corticosteroids or ACTH alone. The profession's challenge to study, immediately and continually, and to control the causative allergies responsible for the antigen-antibody reaction is usually, unfortunately, minimized or ignored. Until the study and orifice of a narrow plastic vaginal barrel, with the tape fixed to its beveled nub by a small ring. Contact is allowed for three minutes with the mucoid cervicouterine and tubal fluid which cascades down the posterior cervical wall (even though the uterus is retroverted) and bathes the posterior vaginal fornix for several days before and during the ovulatory phase of the cycle.

The rod to which the tape is fixed by a small plastic ring is then withdrawn through the protective barrel which prevents the vaginal carbohydrates from coming in contact with the tape. The tape is removed and the underside scrutinized for five minutes. Any color change appearing along even the sides of the tape is significant, for by capillary attraction the glucose solution gravitates to the juncture with the dry tape. If no sugar is present it remains pink; a quantity less than 0.1% will result in pale blue (+); and a quantity of glucose over 0.25% will produce a powder blue color (++). The color change is usually best seen in that portion of the tape which is under the plastic ring. The initial deep blue, indicative of a high (0.25%) glucose value, usually occurs sychronously with ovulation. Occasionally we find it useful to have the patient record her basal oral temperature on a chart each morning and the result of her glucose test below the temperature recording each evening prior to any coitus on every day of the cycle after the cessation of menstrual flow.

One may find that at no time during the month will the tape change color. This may mean an anovulatory cycle. The absence of a thermal shift is confirmation. This is particularly common in women who are having difficulty in becoming pregnant. However, by testing daily, one can tell when these rare infertile periods occur.

If there is a thermal shift it suggests nonegress of the ovum and liquor due to fibrosis or adhesions of the ovarian cortex. Prolonged positive test results may sometimes occur when amounts of estrogens are excessive—e. g., in patients with granulosa cell neoplasm; polycystic ovaries; or pregnancy. If the Testor Tape is used just at the end of the menstrual flow, the vaginal blood sugar may produce a false-positive result—usually a weak reaction which can be avoided by an aqueous douche or bath. It is advisable to inspect the patient's cervix for erosions or polyps before prescribing use of the Fertility Testor Tape, for they minimize the glucose level. If diabetic, bacterial, trichomonal, or monilial vaginitis is present, a hot water douche and drying of the vagina with a tampon will permit satisfactory tests.

Probable Sources of Glucose in the Uterotubal Follicular Fluid Estuary

The glucose present in the cervical mucous cascade may be partly from aspirated liquor folliculi, but some of it is from glycolysis within the fundus [2b] and cervix itself.[2] A recent positive test result from the cervical and cul-de-sac fluid of a patient who had previously undergone supracervical hysterectomy and bilateral salpingectomy without oophorectomy warrants such a conclusion. It seems more likely that during the later days of the presence of a glucose wave pattern, persistence of glucose reaction is due to aspirated liquor folliculi.

The liquor of a mature recently aspirated follicle contained 25.8 mg.% of glucose and gave the typical blue response, as did fluid from the pelvic pool and the tubes. This has been demonstrated in color photography. This technique, therefore, assays the estuary of the uterotubofollicular fluid which is the point of admixture of the isotonic male (ejaculate) and female (uterine cascade) components of the internal fluid menstruum for gametic migration.

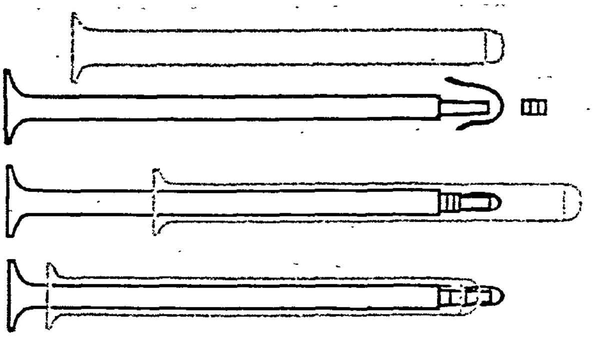

Fig. 1.—*Top,* plunger removed from barrel. Ring at tip of plunger is detached and a precut strip of fertility tape is placed over tip of plunger and secured with retaining ring. *Middle,* plunger is replaced halfway into barrel. Instrument is then inserted into vagina until it reaches apex. During this operation, tape is protected from vaginal secretions that might give misleading coloration. *Bottom,* tip of barrel rests under or against cervix. Plunger is introduced as far as it will go inside barrel, bringing tape in contact with cervix where it comes in contact with any cervical glucose present. Plunger is held in this position for three minutes, then withdrawn from barrel; barrel is removed. Presence of glucose will change color of originally pink tape to blue.

MacLeod [8] has observed maximal acceleration of sperm motility in this mucoid cascade immediately after coitus.

Surgical Confirmation

We have observed 40 infertile women after 4 to 12 months of cervicouterine glucose assay, with simultaneous recording of the thermal shift and the daily fern pattern of crystallization. The disappearance of the fern pattern was noted to lag beyond the period of ovulation. Vaginal smears were difficult to evaluate unless taken from the high lateral vaults. Otherwise there appeared to be a two-to-three-day delay in marked cornification and clumping of the cells. Of five patients who had a negative glucose pattern during the cycle in which they were observed, none had ovulated. Of the 35 patients whose positive glucose

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THE NEW FERTILITY TESTING TAPE

A PREDICTIVE TEST OF THE FERTILE PERIOD

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and
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A test for glucose in mucus from the cervix can be used to indicate the escape of the ovum from the graafian follicle. The glucose fertility test involves paper tape impregnated with glucose oxidase, which catalyzes the oxidation of glucose to gluconic acid. Hydrogen peroxide, a by-product of the reaction, with a peroxidase plus an oxidizable dye changes the tape's pink color to blue. Tested prior to undergoing abdominal operations, 35 women had positive glucose reactions; all were observed during their operations to have ruptured graafian follicles or early activity of the corpora lutea. This relationship was unequivocally proved by careful dating of simultaneous endometrial and ovarian biopsies obtained by culdotomy. Natural child spacing by positive or negative family planning can therefore be carried out inexpensively by intelligent continence on the basis of this evidence of ovulation.

The initial crisis of human genesis occurs within the 12 to 18 hours during and after the escape of the ovum from the graafian follicle. The reduction division of the ovular chromosomes, with the extrusion of the first polar body, has been observed to occur before the ovum escapes from the follicle.[1] Unless the sperm adds its complementary chromosomes, the genetic history of a new human being ends in the first chapter. Man is initially a bifid living entity, composed of two genetically different living units of protoplasm, the gametes. Each is specifically human, yet we die before we ever breathe, unless these physiological bearers of life fuse in the shortest time possible once they start to migrate through the internal fluids of the müllerian tract. The estuary of the female component of this homeostatic internal fluid medium for gametic migration somehow potentiates and stimulates the motility of the sperms. During the preovulatory phase, the cervical mucosa and the endometrium secrete glycogen and other polysaccharides to furnish an extrinsic source of energy for the anaerobic metabolism of the sperms and the ovum and of the conceptus during its six-day journey from the tube into the uterine fluids.

In previous issues of THE JOURNAL,[2] a simple test has been described which registers, by direct visual measurement, the sharp change in reducing substances (increase in glucose) which occurs in the mucous cascade of uterine fluid which usually exudes from the cervix prior to or synchronous with the appearance of ovulation. Glucose has since been demonstrated in the uterine fluid during the ovulatory phase,[3] in the endocervical secretion,[2] in the liquor folliculi of the graafian follicle, and in the pelvic pool.[4]

The principle of the glucose fertility test involves the impregnation of paper tape with glucose oxidase, which catalyzes the oxidation of glucose to gluconic acid. Hydrogen peroxide is a byproduct, and, in the presence of a peroxidase and an oxidizable dye, a blue color is produced.[5] In previous reports, the preparation used was Tes-Tape (Lilly), whose oxidizable dye is orthotolidine.[2] The original observations that glucose could be assayed synchronously from the liquor folliculi of the peritoneal pool and from the endocervical and the exocervical mucous cascade were made with use of Tes-Tape[4] because it had been proved to have a specific reaction to glucose. Recent correlation of this appearance of a wave of cervical glucose with maximal "spinability" of the cervical cascade phenomenon has been reported by Cohen and colleagues,[6] who used the swab technique.[2a] It was deemed advisable to substitute another oxidizable dye for the orthotolidine which was present in the original Tes-Tape because of its chemical similarity to benzidine. The new formula has been approved by the Food and Drug Administration.[7] The use of Tes-Tape, which is now rejected by us, may register sporadic irregular positives.[7] The new fertility tape has no such action.

Details of Technique

To minimize the contact of the fertility tape with glucose originating from the vagina itself, we have successfully used a simple, inexpensive, permanent plastic syringe-like instrument, the Fertility Testor (see fig. 1) designed by one of us (F. J. E.).[2c] This is a plastic rod which is thrust through the

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From the Fertility Clinic, St. Elizabeth's Hospital.

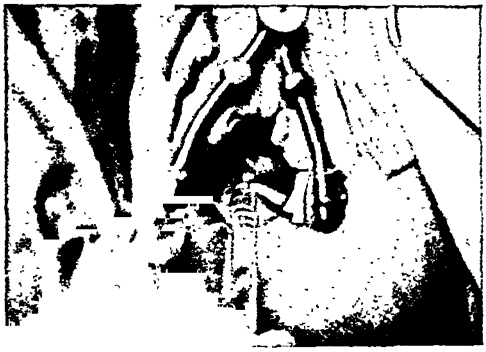

Fig. 2.—Positive result of glucose test from exocervical mucous cascade with use of Fertility Testor. Tape has contacted exocervical cascade which bathes the posterior fornix.

Fig. 3.—Positive glucose test result obtained at culdotomy by contact with pelvic pool of follicular fluid.

Fig. 4.—Positive glucose test result obtained at laparotomy by contact with pelvic pool. Colloid liquor with ovum is exuding from ovary.

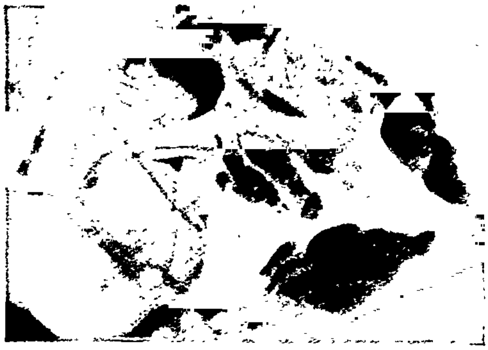

Fig. 5.—Positive glucose test result obtained at laparotomy by contact with tubal fluid and liquor folliculi from recent corpus luteum (hemorrhagicum).

reactions preceded operation, all showed rupturing or ruptured graafian follicles or early active corpora lutea. This relationship was unequivocally proved by careful dating of simultaneous endometrial and ovarian biopsies which were obtained by culdotomy or laparotomy. A confirmatory series of 60 cases will shortly be reported by Kumakiri of Tokyo, Japan.[9]

Relationship to Other Criteria of Fertile Phase.—To the time of writing, during two years' experience with glucose testing of the uterine cascade, we have studied 388 menstrual cycles in 64 women. A more detailed analysis will be published later. The initial appearance of glucose usually preceded the "L" day, that is, the lowest temperature day, by one or two days and occasionally by five days. It may also occur three to four days afterward, during or after the low-to-high shift. It was usually synchronous with subjective mucous discharge and usually preceded ovarian pain when this (infrequently) occurred. This sequence of a subjectively noticeable mucous discharge (2,000 cases), followed the next day by mittelschmerz (1,200 cases) and then the next day by the lowest basal temperature and the thermal shift (9,000 cases), has been reported in a series of 9,000 cycles by R. F. Vollman.[10] It is remarkable that this same pattern persists in our pilot series.

We have recently confirmed with color photography the prompt occurrence of the blue color change of the pink tape when it is applied to the liquor folliculi both if aspirated from or if observed while exuding from mature follicles (fig. 3 and 5). The reaction was also positive synchronously from both the endocervical and exocervical estuary or cascade and also from the pelvic pool, into which the liquor folliculi was observed to flow during culdotomy (fig. 3) or laparotomy (fig. 4), confirming our previous observations.[4] Cul-de-sac puncture and aspiration are simple office procedures to test the pelvic pool for the presence of glucose. We prefer this procedure to the postovulatory but confirmatory disappearance of a fern pattern in the dried cervical mucus.

Advantage Over Basal Waking Temperature Determination for Rhythm Method.—If the woman must be up during the night, her basal waking temperature may be unreliable for determination of ovulation, but the glucose test result is unaffected. Surgical exploration, coordinating the relationship of the thermal shift to the exact occurrence of ovulation, has proved this thermal shift to be not always an accurate indicator of the actual time of ovulation.[11] The recent work of Buxton [11c] in dating recent corpora lutea similarly indicates that there is a period of about five days, two days before, the day of the shift, and two days subsequent to the shift, which probably constitutes the fertility phase. Since fertilization may occur up to 48 hours after coitus (sperm have been known to survive in the tubes for this length of time), it is obvious that the determination of conception time is elusive even by carefully recorded isolated coitus or therapeutic insemination. Yet the prompt occurrence of pregnancy in the series of 23 of 27 fertile women with sterile husbands by single donor insemination (AID) on the first day of the 0.25% glucose-test reaction, as reported recently by Birnberg and Kurzrok,[2a] indicates that this is indeed a simple test available to the fertile and infertile woman either to achieve pregnancy or to postpone the next pregnancy. By the nocturnal precoital use of this new Fertility Testor tape the patient is offered an opportunity of predicting the ovulatory phase of the menstrual cycle with better consistency than by the known capriciousness of the basal thermal shift which may follow or precede ovulation by three or four days, as proved by several series of observations at operation.[11]

Interpretation of Short and Long Positive Glucose Reactions

The persistence of the usual five-to-six-day glucose pattern is probably due to aspirated liquor folliculi passing through the tubes and the uterus. Hence, a short, scant glucose pattern may possibly signify ovarian cortical fibrosis or tubal patency variations due to kinks, adhesions, or uterotubal spasm. It may also signify a hormonal target organ defect, for example, uterotubal hypoplasia. We have twice photographed the occurrence, during operation, of double ovulation from the same ovary during the same cycle. A double wave of glucose had been observed by the Fertility Tape. Since this recurrent ovulation was not suggested by the basal thermal shift, and since it can only be detected, at present, by the use of the sensitive glucose test, we believe that any patient in whom it is imperative to use periodic continence had best constantly record daily glucose determinations throughout the cycle. We have observed glucose patterns preceding the "L" day to be consistent in commencing on day 11 to day 15 for four months only to shift to day 7 (proved by pregnancy after isolated coitus), yet the menstrual cycle variation was only 27 to 29 days.

Since ovulation has occurred on days 7 and 24 in the same patient, with a menstrual variation cycle of 21 to 35 days, it is obvious that such a concurrent test for the fertile phase is definitely indicated. Since emotional factors cause unpredictable marked variations in menstrual rhythm, it is extremely important to assure the patient on the basis of her present condition and not of her past or unpredictable future status. In protecting invalid mothers from pregnancy which would be more wisely postponed in the interest of her health, it has been our previous practice not to permit any coitus until four days after the "plateau of the square root sign" (√) of the basal temperature chart. It seems wise, therefore, for such patients to avoid coitus until all blue reaction has been absent for at least three days. No nutrient glucose is then available for the gametes or the conceptus.

Hertig and colleagues[1b] recently stated that ovular loss is greatest in the preimplantation stage and that maximum fertility rate at the time of ovular implantation is only 58%. It seems rational to aid the physiological substrate by making use of the known "glucose tide." In patients in whom glucose is minimal we are now introducing sterile 0.25% glucose solution in normal saline by trans-uterotubal lavage or cul-de-sac puncture insertion.

Accordingly, natural child spacing by positive or negative family planning is now more feasible at minimal cost and without moral scruples. Intelligent continence, with visual cognizance of ovular longevity, suffices.

Comment

The fertility tape, which demonstrates the time of the escape of follicular fluid, is a practical indicator of the time of the presumed escape of the egg from the follicle itself.[4] It seems logical that calculation of any mathematical relation in which the "constant" lies in the future (like ordinary rhythm by the calendar method) is less scientific than concurrent calculation of the actual ovulation itself.[4] The postpartum patient in poor health will have greater peace of mind if she is told that she cannot conceive in this cycle here and now under consideration if she omits coitus for at least three days after the glucose test result has ceased to become positive (blue). Periodic continence until after the ovum has ceased to exist as a biological entity offers a phase of the menstrual cycle during which pregnancy would be a biological impossibility if secondary ovulation does not occur.[2b] The glucose pattern of two such double-ovulatory patients confirmed by operation was such that it appears that such an event occurs within a matter of one to three days. This is logical, since the hormone levels within the ovary would affect each follicle simultaneously. The temporal delay seems to be due to the initial depth of the maturing follicle rather than to the width of the cortex of the ovary. When fibrosis of the ovarian cortex prevents egress of the glucose laden liquor and ova, the scant or absent glucose tide offers a new test for intraovarian nonmigratory ovulation. The thermal shift is positive; the ovulation is painful. A buried corpus hemorrhagicum was recently revealed during performance of a wedge resection. Further statistical series must be observed, however, before definite conclusions can be drawn. By the same reasoning, the infertile couple may be offered new hope by postponing postmenstrual coitus until the fertility testor gives visual evidence that the nutrient glucose is available. It is an indirect indicator that the other salutary enzymes are now available and that the mucous cascade is more profuse, watery, and penetrable to the sperm.[8] The man with oligospermia needs optimal pH and miscibility of the male and female components of the flumen vitae.[2b]

Summary

In a predictive test for the fertile phase of the menstrual cycle, which assays the glucose content of the exocervical mucous cascade, the indicator is a new Fertility Testor tape in which a double-enzyme system of glucose oxidase and a peroxidase are used. No orthotolidine is present. The color reaction observed is a change from pink to blue. It usually occurs from one to three days prior to ovulation, as determined by simultaneous biopsy of the endometrium and corpus luteum, and it usually persists for one to four days after ovulation. A prolonged or recurrent color reaction suggests a secondary ovulation, which has been confirmed at operation. The test is simple, inexpensive, and more readable than basal temperature charts and the now rejected Tes-Tape indicator.

Positive tests have uniformly been observed prior to and during ovulation from the exocervix, endocervix, and the follicular fluid and early corpus luteum fluid and from the immediate postovulatory pelvic pool. Infertile patients should commence coitus on the first day of the blue phase. Overfertile patients for whom periodic abstinence (rhythm method) is indicated should postpone coitus until three days after the disappearance of the blue reaction. Precoital aqueous douches and the use of the Fertility Testor will eliminate contamination by vaginal secretion.

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The Fertility Testor Tape used in this study is available from the Fertility Testor Company, Ottawa, Ill.

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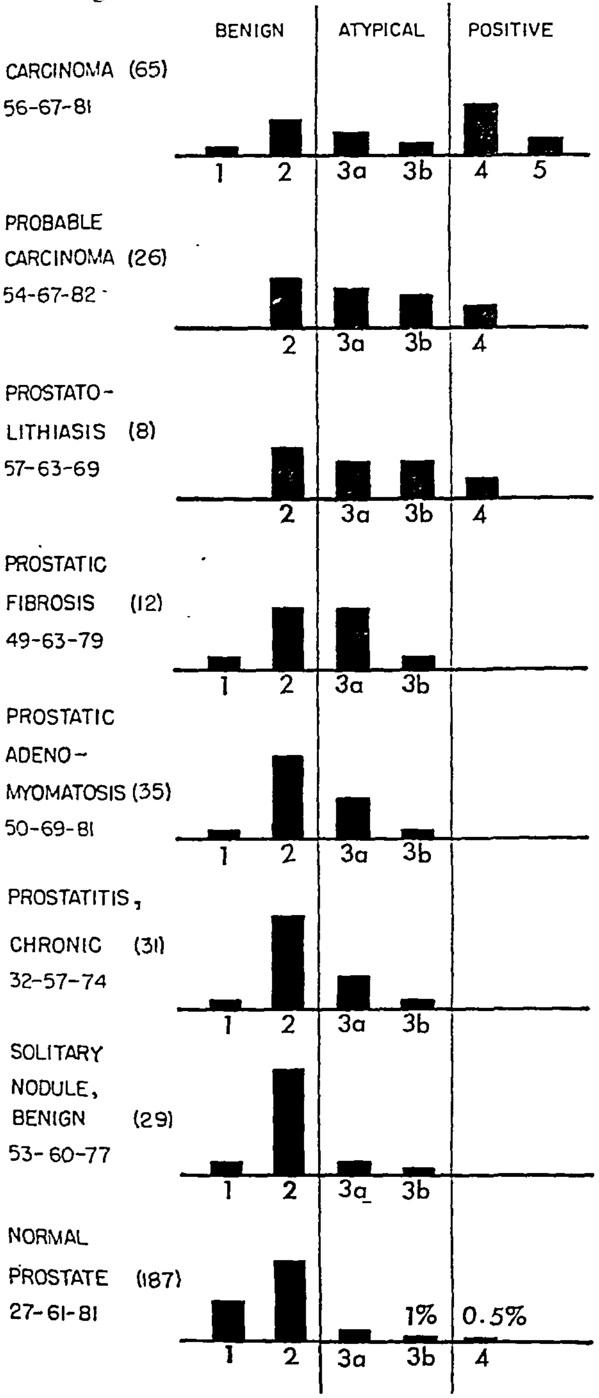
(*d*) typical reaction to endocrine treatment; or (*e*) histological evidence of malignancy, obtained by perineal needle biopsy, perineal surgical biopsy, radical prostatovesiculectomy, or autopsy.

The numbers, average ages, and age ranges of the patients in each diagnostic category are indicated in the figure.



Percentage distribution of cytological interpretations of smears of prostatic fluid. Number of patients in each category appears in parentheses. Other numbers indicate, respectively, age of youngest, average age, and age of oldest patient in each diagnostic category.

Results

The figure depicts the results of study of the 393 smears which were considered to be of adequate quality for interpretation and classification. The incidence of false-negative interpretations was 54% and of false-positive interpretations 0.5%.

The one patient with a presumably normal prostate and what was considered an adequately substantiated false-positive interpretation (class 4) was 42 years of age. In this patient total prostatovesiculectomy as the only means of conclusive diagnosis is considered unwarranted.

Twenty-nine patients had solitary prostatic nodules which one of us (B. G. C.), without knowledge of the cytological findings, classified as benign on the basis of rectal palpation.[5] In this group of patients no class 4 or 5 reading was recorded.

Among the patients with chronic prostatitis, adenomyomatosis, and fibrosis, the incidence of atypical readings was fairly high. It was even higher in patients with prostatic stones. The patient with a class 4 reading in the latter group was a 67-year-old man, with typical prostatic stones, who has been under observation since 1954 without exhibiting objective evidence of carcinoma.

TABLE 1.—*Cytodiagnosis in Histologically Proved or Clinically Certain Prostatic Carcinoma*

Source	Cases, No.	Diagnosis		
		Positive	Suggestive	Negative
Albers and others*†	24	21	...	3
Boyer[8]	24	16	3	5
Clarke and Bamford (present study)‡	65	30	16	19
Fergusson and Gibson[9]†	38	34	2	2
Gunn and Ayre[10]*	26	19	...	7
Hock and others[11]	13	4	4	5
Peters and Frank[12]	100	88	7	5
Reese[13]	14	10	1	3
Williams and Nieburgs[14]*	20	14	...	6
Total	324	236	33	55§

* No data on suggestive smears

† Hematoxylin-eosin stain.

‡ Data based on number of smears.

§ 17% of smears false-negative.

Comment

Tables 1 and 2, collected from publications on the cytological diagnosis of prostatic malignancy, indicate that 17% or more of false-negative smear interpretations may be expected to occur. The incidence of false-positive readings is about 0.3%.

To be of value to the cytologist, secretion must be collected from the prostate in sufficient quantity by correctly performed massage. Most of the secretions from normal glands were collected by examiners without special training in prostatic massage. Forty-five per cent contained insufficient cellular material for diagnosis. Occasionally, hard, frankly malignant glands yield scant secretion,[6] although in such cases other means are usually available to substantiate the diagnosis.

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CYTOLOGY OF THE PROSTATE GLAND IN DIAGNOSIS OF CANCER

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and
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The study of cytological smears is of recognized usefulness in diagnosis of neoplasms of the cervix, lung, stomach, and certain other sites but has not, in spite of suggestions in early reports,[1] been widely used in detection of prostatic cancer. Experience with prostatic cytodiagnosis from 1953 to 1959 at the New England Medical Center is reported, with a review of available literature, in the present study.

Materials and Methods

The reports of 543 smears made from the prostate glands of 442 patients were correlated with available clinical information. Three hundred ninety-three preparations, from 306 patients, were considered to contain sufficient cellular material for reliable interpretation. Smears were collected by prostatic massage,[2] stained by Papanicolaou's method,[3] and interpreted by one of us (S. B. B.). Interpretations were classified as 1 (normal), 2 (benign pathology), 3a (atypical; repetition of examination suggested), 3b (atypical; suggestive of cancer), 4 (positive, biopsy advised), and 5 (positive, conclusive).

On the basis of all available clinical, roentgenographic and laboratory findings, the prostate glands were classified as follows: normal; solitary nodule, benign; prostatitis, chronic; prostatic adenomyomatosis; prostatic fibrosis; prostatolithiasis; probable carcinoma (rectal findings suggestive but conclusive diagnostic evidence lacking); and carcinoma.

Cellular material, considered sufficient for reliable cytological interpretation, was obtained by prostatic massage from 306 male patients. The strictly cytological results, ranging from class 1 (normal) to class 5 (conclusively positive for carcinoma), were then compared with the combined results of all other available clinical, roentgenographic, and laboratory findings. A false-positive diagnosis of carcinoma occurred only once. In the assembled data of the authors and of previous investigators, false-negative cytodiagnoses have occurred 55 times in 324 cases. Some hard, frankly malignant glands yield insufficient secretion. The authors believe that palpation remains the best means for diagnosing prostatic carcinoma in its early asymptomatic stages, but cytodiagnosis, yielding few false-positive results, is of great corroborative value in the diagnosis of inoperable prostatic cancer.

One or more of the following criteria were observed in every patient classified in the category carcinoma: (*a*) classical rectal findings (woody-hard infiltrative changes, whether intracapsularly localized or not); (*b*) typical roentgenographic evidence of osseous metastasis; (*c*) significant elevation of the serum acid phosphatase level, estimated by the King-Armstrong or Fishman-Lerner[4] methods, or both;

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RADIOACTIVE PHOSPHORUS IN THE IN VIVO DIAGNOSIS OF MELANOMA OF THE SKIN

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Pigmented and nonpigmented lesions in 49 patients were studied to determine the reliability of a test based on the concentration of intravenously injected radioactive phosphorus (P^{32}) in such lesions. Counts were made frequently over a three-hour period at the site of the tumor and were compared with counts made at a contralateral normal site in the same patient. Two illustrative cases are described. In the first case the result of the test was positive and the lesion when excised proved to be a melanoma. In the second case, however, results of the test suggested a melanoma but the excised tumor proved to be a benign sclerosing hemangioma. In the entire series there were 20% false-positive and 37% false-negative results. In its present form this test cannot be relied on to distinguish melanomas from other skin tumors.

The practicing physician is frequently called on to differentiate between benign and malignant skin tumors. Clinical examination alone of the lesion is often sufficient to provide the answer, although, at times, special techniques and laboratory procedures, including biopsy, may be necessary to establish the diagnosis. Among these tumors are many pigmented cutaneous neoplasms which the physician sees daily and which present no real diagnostic problem. However, there is also the occasional pigmented lesion which has features suggestive of malignant melanoma (hereafter referred to as "melanoma") but in which this diagnosis cannot be made with certainty on clinical grounds alone. To cut through such a doubtful lesion to obtain a biopsy specimen for histopathological study is considered by some authors [1] to increase the risks of spread and metastasis, and most authorities express the opinion that total excision, with wide margins, should be performed initially if melanoma is suspected.[2]

Among the pigmented lesions that clinically may be confused with melanoma, the most frequent is the pigmented cellular nevus: the term "pigmented nevus" will be used in this paper to include only those nevi containing nevus cells. Since these are commonly found on such cosmetically and functionally important areas as the face,

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Read before the Section on Dermatology at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 12, 1959.

In men over 50 years of age without clinical evidence of prostatic carcinoma detailed microscopic study of the gland at autopsy shows foci of tissue with the histological appearance of cancer in 14 to 50% of cases.[7] In our group of normal patients, whose average age was 61 years, cytological findings did not correspond with these data.

Our experience appears to warrant the conclusion that rectal palpation of the prostate in patients over 50 years of age remains the best means for diagnosing carcinoma in its early asymptomatic stage when it is still curable by radical prostatectomy. Palpation is also as accurate as any single available method for diagnosis of inoperable prostatic cancer requiring palliative treatment. Elevation of the serum acid phosphatase level measured by standard or fractionated methods is useful corroborative evidence of prostatic cancer. In no case of localized, operable cancer in the present study were abnormal results recorded from the phosphatase tests.

Table 2.—Cytodiagnosis of Presumably Normal Prostate Glands

	Cases, No.	Smear Positive; Cancer Detected and Subsequently Proved	Clinically or Histologically Substantiated False-Positive
Albers and others[6]*	100	3	0†
Boyer[8]	137	0	0†
Clarke and Bamford‡	187	0	1
Fergusson and Gibson[9]*	57	2	2
Frank[15]	1,052	8	5
Gunn and Ayre[10]	500	5	0†
Herbut and Lubin[1d]	100§	1	1
Hock, Wood, and Kosinski‖	137	2	2
Reese[13]	335	3	1
Williams and Nieburgs[14]	1,259	11	0†
Total	3,963	38	12‖

* Hematoxylin-eosin smears.
† None reported.
‡ Data based on number of smears.
§ Some of patients had pathological prostates.
‖ 0.3% false-positive smears.

Cytodiagnosis yields few false-positive results and is of corroborative value for diagnosis in patients with inoperable prostatic cancer. Its use, when the lesion remains localized within the prostate and surgically curable, may be criticized on the ground that vigorous massage of the gland to procure material for smears may disseminate the lesion throughout the vascular and lymphatic systems. Perineal or transrectal punch or needle biopsy of the prostate, although a negative result does not exclude cancer, is an acceptable means of securing tissue for histodiagnosis in patients with inoperable cancer. In patients with localized operable lesions these biopsy techniques should be used cautiously or not at all, since viable cancer implants can grow in the track of the biopsy instrument and because negative results are inconclusive. One instance of such cancer transplantation occurred among the patients studied by us and reported elsewhere.[16]

In patients presenting palpable prostatic nodules with characteristics suggesting malignancy yet which are localized within the confines of the gland, surgical exposure by the perineal or retropubic route, biopsy if necessary, and radical prostatovesiculectomy if indicated are the only conclusive means of diagnosis. This approach to operable prostatic cancer may be expected to yield, as Jewett,[17] Turner and Belt,[18] and Colston [19] have shown, 5-year and 10-year survival rates nearly approximating the life expectancy of normal men of comparable ages.

Summary

Cytological interpretations of 543 smears of prostatic fluid obtained from 442 patients were correlated with clinical information. Among patients with carcinoma of the prostate 46% of smears were positive (class 4 or 5). Among normal persons, 0.5% of false-positive smears occurred. Atypical cellular material was found in a relatively high proportion of patients with chronic prostatitis, fibrosis, adenomyomatosis, and particularly among patients with prostatic calculi.

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Dr. Joseph J. Kaplan, Medical Director, Union Health Clinic, United Ladies' Garment Workers of America, Boston; Dr. Kaplan's associates and staff members of the New England Medical Center gave permission for inclusion of their patients in the study. Misses Joan Grady, Helene Robinson, and Helen Minihane gave help in collecting and analyzing statistical material. Drs. Howard E. MacMahon and Gherardo Gherardi carried out histodiagnostic correlations.

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original report, the surface radioactivity (counts per minute) of the cutaneous melanoma sites was 2.5 to 3.85 times greater than the surface radioactivity of the contralateral normal skin (control) sites. However, in our subsequent correspondence with Bauer,[5] he stated that "on several cases of proven malignant melanomas . . . the increases were only on the order of 30% (1.3)." (This figure [1.3] refers to the increase in surface radioactivity [counts per minute] at the melanoma site compared to the control normal skin site.)

On the hope that their method might aid us to differentiate in vivo between benign pigmented lesions and melanoma, we set out to study a group of patients with Bauer's and Steffen's[3] test procedure. Our efforts were further stimulated by other encouraging reports about the uptake of radiophosphorus in melanoma which appeared from time to time in the literature.[6]

Subjects and Procedure

Selection of Patients.—Patients suspected of having melanoma or lesions likely to be confused with melanoma were chosen for study from the Oncology Section of the Skin and Cancer Unit. In addition, a wide variety of lesions including vascular (e. g., hemangiomas), granulation (e. g., granuloma pyogenicum), and other benign and malignant skin tumors were selected (table 1). None of the epitheliomas included in our series was fungating.

Test Procedure.—Each patient chosen for study was placed at rest on a table. The lesion in question was marked off with ink, and a symmetrical but normal skin site on the contralateral side was selected for control measurements and similarly marked off. Prior to administration of the radioactive phosphorus solution, a count of the naturally occurring background radioactivity of the room was made; this was followed by "background" counts taken over the lesion and over the control site in question. All counts were made with a thin, end-window Geiger-Müller probe, connected to a count ratemeter which automatically indicates the radioactivity in counts per minute (cpm). A thin sheet of Mylar (polyester film) (0.9 mg. per square centimeter) was interposed between the skin and the Geiger-Müller probe to avoid contamination of the window of the latter. To limit the survey (the amount of measurable radioactivity obtained, expressed in counts per minute) to the immediate tumor area, adapter shields made of Lucite, with inserts of lead that have apertures of various sizes, were used over the end-window of the Geiger-Müller probe and against the skin (fig. 1). The contralateral normal skin site was similarly surveyed. Surveys were made after each patient had been given about 150 μc of radioactive phosphorus in 10 ml. of aqueous solution by intravenous injection. (P^{32} has a half life of 14.3 days and is a pure beta emitter, whose particles have a maximum soft-tissue penetration of about 7 mm., with an average of about 2.5 mm.[6b]) The counting procedure at both the tumor and control sites was repeated at frequent intervals over a three-hour period of observation. During the first half-hour of observation, while the radioactive uptake by the tumor was increasing, readings usually were taken at 3-minute to 10-minute intervals. When the readings (counts per minute) over the test site remained the same or began to diminish, observations were made at longer intervals. Each reading was taken directly from the count ratemeter when the needle had stabilized, usually 15 to 60 seconds after the Geiger-Müller probe had been placed in position over the lesion. In this manner, 145 individual lesions (in 49 patients) were surveyed and the results compared with readings taken over contralateral, apparently normal skin (control) sites. Since this study was undertaken primarily for the in vivo diagnosis of melanoma, the lesion was completely excised for histological examination in all instances in which this diagnosis was suspected either by clinical examination or by the P^{32} testing procedure.

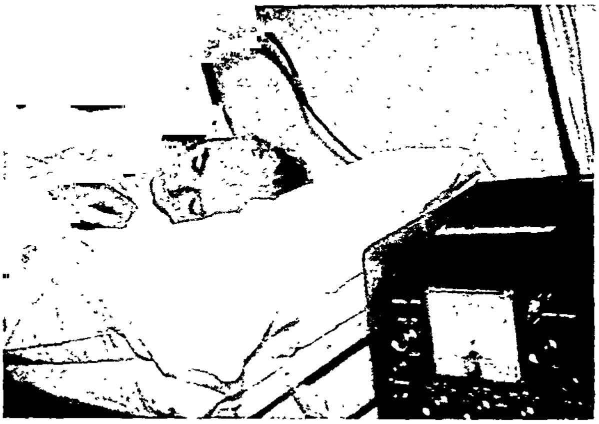

Fig. 1.—Test procedure: Geiger-Müller probe, with Lucite adaptor and Mylar film covering probe end-window taped onto tube housing and held in place over test site. Count ratemeter is in lower right-hand corner.

Analysis of Data

The test procedure as outlined provides a comparison of the surface radioactivity[7] at the site of the tumor versus the surface radioactivity over a contralateral normal skin (control) site. The result of this comparison may be expressed as a ratio, which is determined as follows:

Ratio (relative surface radioactivity) = (tumor site count less background count) ÷ (control site count less background count).

The following example from our series will serve to illustrate a "positive" result (according to Bauer and Steffan[3]).

Case 1.—A 65-year-old housewife had a slowly enlarging brownish-black discoloration on the outer aspect of her right arm, of seven years' duration palms, and soles, the dictum to excise widely every such suspicious lesion imposes a great responsibility on the physician.

The need for a dependable in vivo method for accurate differentiation between pigmented melanomas and pigmented benign lesions that resemble melanoma prompted us to repeat the investigations of Bauer and Steffen.[3] These authors reported that their technique, with use of the intravenous administration of radioactive phosphorus (P^{32}), enabled them to differentiate between melanomas and benign skin tumors; melanomas showed a significantly increased concentration of radioactive phosphorus (P^{32}) in comparison with normal skin and the other skin lesions studied.

This differential uptake of P^{32} has been explained by the fact that, in the more metabolically active tissues, such as neoplastic tissues, there is an increase in mitotic activity, and the concentration and turnover of nucleoproteins (of which phosphorus is a constituent) is greater. Consequently, the radiophosphorus is taken up in relatively greater amounts and held longer in certain neoplastic tissues.[4]

With their technique Bauer and Steffen[3] found that, in a series of patients with tumors of the skin, which included 11 cutaneous melanomas, studies yielded "no false-positive or false-negative results," provided deep-seated melanomas, granulation tissue, fungating basal cell carcinomas, and epidermoid carcinomas were excluded. According to their

TABLE 1.—*Skin Lesions Studied After Intravenous Administration of Radioactive Phosphorus* (P^{32})

Type of Lesion	No. in Group (Total 145)	Number of Lesions and their Ratios (Relative Surface Radioactivity)* 0.6-0.7	0.8-0.9	1.0-1.1	1.2-1.3	1.4-1.5	1.6-1.7	1.8-1.9	2.0-2.1	2.2-2.3	2.4-2.5	2.6-2.7	2.8-2.9	3.0-3.1	3.2-3.3	3.4-3.5	3.6 and over
Cutaneous melanoma																	
Primary	11	..	..	2	..	2	..	3	..	2	..	..	..	..	..	..	2
Metastatic	13	..	..	1	4	2	..	..	..	1	..	..	..	1	..	1	..
Subcutaneous melanoma†	3	..	1	2	..	..	..	..	..	..	..	..	..	..	..	..	..
Basal cell epithelioma	3	..	..	..	..	..	1	..	..	2	..	..	..	..	..	..	..
Epidermoid carcinoma	2	..	..	1	..	..	..	..	1	..	..	..	..	..	..	..	..
Skin metastases of ductal tumor, not otherwise specified	2	..	..	1	..	..	..	..	..	1	..	..	..	..	..	..	..
Lymphosarcoma	4	..	..	..	4	..	..	..	..	..	..	..	..	..	..	..	..
Benign lesions with melanin pigmentation prominent	68	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Acrochordon	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..
Pigmented nevi	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Blue	..	1	..	1	2	..	..	..	..	..	..	..	..	..	..	..	..
Compound	..	..	3	12	4	..	..	..	..	..	..	..	..	..	..	..	..
Intradermal	..	..	3	3	2	..	..	..	..	..	..	..	..	..	..	..	..
Intraepidermal	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..
Junction	..	..	3	13	3	1	..	..	..	..	..	..	..	..	..	..	..
Lentigo	..	..	..	2	1	..	..	..	..	..	..	..	..	..	..	..	..
Ephelis	..	..	1	1	..	..	..	..	..	..	..	..	..	..	..	..	..
Melanotic freckle	..	..	..	2	2	..	..	..	..	..	..	..	..	..	..	..	..
Keratosis seborrheica	..	..	1	1	..	..	..	..	..	..	..	..	..	..	..	..	..
Keratosis senilis	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..
Benign lesions with melanin *pigmentation not prominent*	39	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Blue tattoo	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Callus	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Contusion	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..
Cutaneous horn	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..
Fibroma	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..
Cutaneous (fibrous) nevus	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..
Grafted skin	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..
Granuloma pyogenicum	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..
Hemangioma	..	..	..	1	1	..	..	..	..	..	..	..	..	..	..	..	..
Spider hemangioma (nevus araneus)	..	..	..	1	1	..	..	..	..	..	..	..	..	..	..	..	..
Nodulus cutaneous	..	..	1	5	1	..	1	..	..	1	..	1	..	..	..	1	..
Scar	..	..	1	3	..	1	2	..	..	..	..	..	..	..	..	..	..
Sebaceous nevus	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..
Senile angioma	..	..	..	3	1	..	..	..	..	..	..	..	..	..	..	..	..
Sweat gland adenoma	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..
Varicose vein	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Verruca vulgaris	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..
Werther's *nevus*	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..

* Ratio (relative surface radioactivity) is the comparison of the number of counts per minute over the tumor site to the counts per minute over the contralateral normal skin control site.

† By subcutaneous is meant any lesion wholly within or below the subcutis (e.g., lymph node metastases). It should be noted that subcutaneous melanomas have been separated from the cutaneous melanomas since most of the former lesions lie too deep to be measured for their radioactive uptake of P^{32}. Even the strongest beta particles of P^{32} are capable of penetrating only about 7 mm. of soft tissue.

could be compared to the "general population," namely, those with all other disease groups combined.

The estimated standard deviation for each reading was calculated from the length of time that each reading was observed (15 to 60 seconds) and the time constant of the count ratemeter. The net readings for both tumor and control sites were obtained by subtracting the background reading from the original readings at tumor and control sites. The standard deviation for the net reading was also calculated as the square root of the sum of the squares of the standard deviations of the original readings.

The net readings at tumor and control sites were then plotted on semilogarithm-graph paper for the various time intervals at which the counts per minute were recorded. Smooth parallel lines were drawn through the two sets of data. On a logarithmic plot, parallel lines correspond to a constant ratio. An estimate of the ratio of tumor site to control site was obtained from the smoothed parallel lines (in the interval, usually of 30 to 180 minutes). The standard deviation for the value of the ratio was obtained by statistically compounding the estimated errors for each smoothed line. The frequency distribution of the different ratios was then plotted, and standard deviations for the population and the error of the mean were calculated. It was found that most of the individual ratios obtained had a standard deviation considerably lower than that for the entire population. Ratios that had errors comparable to the standard deviation of the population were given appropriately low statistical weights in calculating the mean of the population and its standard error. The same procedure was also followed when the "population" was broken down into groups. These data are summarized in tabular form (table 3).

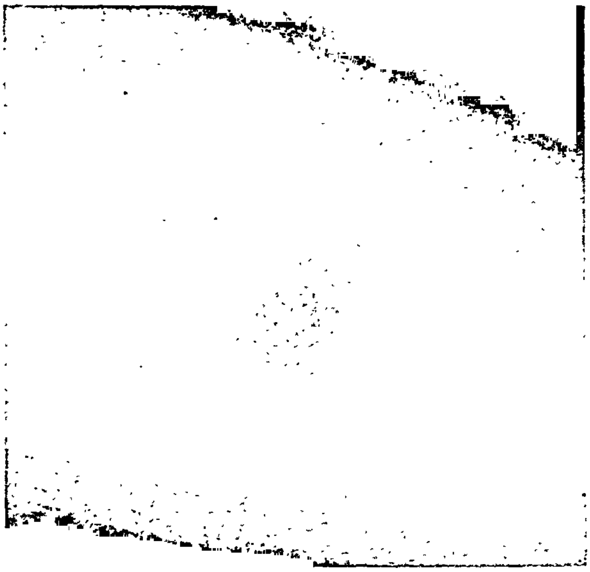

Fig. 3 (case 2).—Cutaneous nodule (sclerosing hemangioma) on right leg.

Comment

If one accepts ratios of surface radioactivity (tumor/control) as low as 1.3 as diagnostic of cutaneous melanoma, our test conclusions would have resulted in our making the diagnosis of cutaneous melanoma 20% of the time in the "general (control) population." That is to say, the tests would have yielded false-positive results in one-fifth of the patients in our series. Even more important is the finding that in our patients with cutaneous melanoma the test would have been correct in only 63% of the cases (37% were false-negative determinations). If one were to increase the diagnostic ratio, e. g., to 1.8 or 2.0, the number of false-positive results would diminish; however, at this ratio the number of false-negative results would be increased.

TABLE 3.—*Comparison of Means of the Ratios* of Surface Radioactivity in Various Groups of Skin Lesions After Radioactive Phosphorus (P^{32}) Uptake*

Lesion		P^{32} Uptake		
Group	Total No.	Mean of Ratios*	Standard Error of Mean	Standard Deviation of Population in Disease Group
I. Cutaneous melanoma	24	1.87	±0.16	±0.79
II. Lesions other than cutaneous melanoma				
Subcutaneous melanoma ...	3	0.97	...†	...†
5 basal cell epitheliomas and epidermoid carcinomas; 2 skin metastases of breast carcinoma	7	1.67	±0.22	±0.55
Lymphosarcoma	4	1.28	...†	...†
Benign lesions with pigmentation as prominent feature	68	1.08	±0.02	±0.14
Benign lesions without pigmentation as prominent feature	39	1.24	±0.05	±0.28
Total (group II)	121	1.18	±0.04	±0.39

*Ratio is comparison of number of counts per minute over tumor site to counts per minute over contralateral normal skin (control) site.
†Groups too small to permit statistical analysis.

That the use of this test procedure by us could not be depended on to differentiate regularly between cutaneous melanomas and the other skin tumors studied can be explained on examination of the distribution of the ratios determined for all lesions (fig. 4). Although the mean of the ratios of the cutaneous melanoma group is higher (1.87) than the mean of the ratios of the "general population" (1.18), the overlap which takes place in the distribution for both groups is sufficiently great so that, in many instances, one cannot conclude, on the basis of the ratio of the surface radioactivity alone, whether the lesion in question falls within the cutaneous melanoma group or into the "general population" group.

(fig. 2). One year prior to admission to the clinic, the surface of the "freckle" became scaly and crusted, and eight months later the central portion of the lesion showed some loss of pigmentation. Shortly thereafter a small, black elevation appeared near the center of the "freckle." When first examined in the Oncology Section, the lesion was roughly circular, about 5 cm. in diameter, and had an intense, brownish-black discoloration with a well-defined but irregular border that showed a slight inflammatory halo. Several depressed areas near the center of the plaque showed depigmentation and atrophy. Near the center of the lesion was a 3 by 5 mm. raised, blackish, crusted nodule. The regional axillary lymph nodes were not enlarged. The counts per minute that were obtained are shown in table 2.

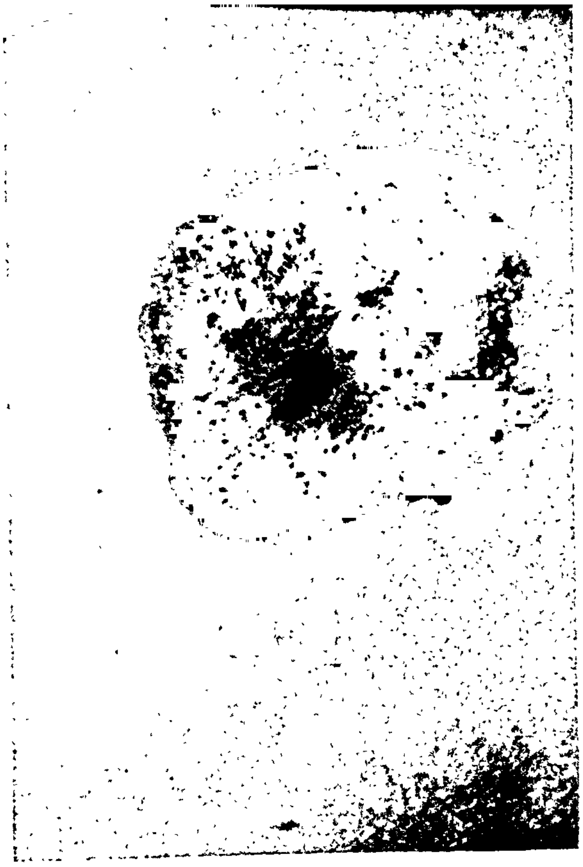

Fig. 2 (case 1).—Melanoma of right arm.

If one takes the greatest differential in counts per minute that were observed between the tumor site and the contralateral normal skin site (regardless of the elapsed time) and corrects for background (90 cpm), the ratio of the counts is 1,360/230, which is about 6 (ratios will be expressed as single numbers, i. e., a ratio of 6 represents 6:1). According to Bauer's and Steffen's reported findings, ratios of 2.5 (more recently 1.3) and greater have been noted for melanoma. Consequently, on the basis of the ratio of 6 obtained in this case, one could conclude that the lesion was a melanoma. Indeed, when the lesion was completely excised, the histopathological findings confirmed that diagnosis. Should this finding of a high ratio of surface radioactivity for melanoma occur in several observations, it would be easy to assume that an interdependent relationship exists, i. e., that the demonstration of a high ratio always indicates a melanoma.

Positive findings such as these were encouraging, but, early in our study, a patient examined by the same procedure gave a false-positive response. The patient's medical history and the description of the lesion in this case are as follows:

Case 2.—A 70-year-old waitress had a nodule of 35 years' duration at a site of trauma on the anteromedial aspect of her right leg. The mass had not changed its characteristics during those many years. The lesion was a kidney-shaped, firm, elevated, yellowish-red intracutaneous nodule which had some darker brownish-black areas (fig. 3). The clinical diagnosis was fibroxanthoma (lipoidal histiocytoma). The largest ratio of surface activity was 2.9, which suggested the possible diagnosis of melanoma, and, therefore, the lesion was widely excised. Histological study of the excised specimen, however, revealed the lesion to be merely a benign sclerosing hemangioma (cutaneous nodule). The occurrence of this false-positive finding, together with others, and the appearance also of several false-negative results among some patients in our series prompted us to subject all of our accumulated data to statistical analysis.

While this study is based on the fact that certain living tissues take up radioactive phosphorus in a selective manner, there are numerous variables in a study of this type which make statistical analysis necessary. For example, radioactive disintegration itself is a random phenomenon, and the accepted methods for measuring this random phenomenon have many variables of their own. Also, there probably are many systemic as well as local biological factors peculiar to an individual person which may account for significant variation in radioactive phosphorus uptake. Furthermore, there may be inherent differences not only among patients but between contralateral sites in the same patient.[66]

Table 2.—*Surface Radioactivity (Counts per Minute) of a Melanoma Compared with Normal Skin After Intravenous Administration of Radioactive Phosphorus (Case 1)*

	Elapsed Time, Min.	Tumor Site, Cpm	Contralateral Normal Skin Site, Cpm
Preinjection	...	99	90
Postinjection	0	Injection of 150μc of P^{32}	0
	2	170	160
	12	1,450	320
	60	1,250	430
	100	1,300	410
	140	1,250	380
	165	1,250	450

The lesions were divided into groups (table 3) or separate "populations," so that the results from the group of those with proved cutaneous melanoma

STERILIZATION OF INSTRUMENTS AND MATERIALS WITH BETA-PROPIOLACTONE

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Most substances used for sterilizing surfaces at room temperatures do not kill bacterial spores. Beta-propiolactone (BPL) is a liquid which exerts a strong bactericidal action on the surfaces of objects immersed in aqueous solutions of it or exposed to its vapor phase. In the present experiments it was used in three ways, being vaporized by heat in air at atmospheric pressure, vaporized at room temperature under reduced pressure, and applied as an aerosol by means of nebulizers. Five test-organisms, including Clostridium sporogenes, were used, and a variety of instruments heavily contaminated with them were sterilized at room temperature. In addition, practical experience with a wide variety of apparatus has been accumulated over a period of 16 months. Beta-propiolactone has a broad field of application provided its limitations are recognized and it is handled, like other bactericidal agents, with due regard for its toxic properties.

Modern medical and surgical practice uses many devices and materials which would be impaired by exposure to saturated steam or to hot air at sterilizing temperatures. Optical, electronic, and mechanical devices such as cystoscopes, radiation counters, and oscillating saws fall into this category. Many plastics and certain forms of rubber present similar problems. Because these devices and materials may come in contact with open wounds, disinfection or sanitization cannot be substituted for a true sterilizing process.

Most substances used for "cold sterilization" are not sporicidal and are therefore not true sterilizers. As Spaulding [1] has pointed out, there is a significant difference between the resistance of certain spores and that of the vegetative bacteria which produce these spores. Selection of resistant spores for sterility testing should be limited to suspensions containing spores which survive exposure to constant-boiling hydrochloric acid for 30 minutes or more. Spore counts should be made only after pasteurization of the suspension to kill all vegetative forms. Spore suspensions should be allowed to dry on carriers.

Not only a susceptible test organism but also an inadequate sterility test medium can lead to a false conclusion that a sterilizing process has been effective. By adding horse serum to the sterility test medium Klarmann [2] has shown that an apparent sporicidal effect after eight hours' exposure to a formaldehyde germicide was merely sporistatic. We have evidence [3] that fluid thioglycollate medium may fail to demonstrate germination of chemically insulted but still viable spores.

Most germicides have merely a disinfectant or antiseptic effect. No germicide having a rapidly lethal effect on resistant spores has found wide use up to the present time. More serious than mere lack of sporicidal effect have been instances of Pseudomonas contamination of quaternary ammonium compounds used as cationic germicides.[4] In ophthalmic surgery, such instances have had disastrous consequences. In all branches of surgery, the possibility of transmitting infection by means intended to prevent it must be excluded.

The ideal gaseous sterilizer, according to Lloyd and Thompson [5] would be as follows: (1) noncorrosive; (2) harmless to materials; (3) penetrative; (4) easily removed by aeration; (5) rapid in action; (6) low in toxicity to human beings and animals; (7) nonflammable and nonexplosive; (8) convenient to store; (9) readily available commercially; (10) inexpensive; and (11) bactericidal, sporicidal, virucidal, and fungicidal at ordinary atmospheric conditions. We shall examine the extent to which some of these properties are held by the common gaseous sterilizers.

Formaldehyde and, more recently, ethylene oxide have been used as gaseous disinfectants or sterilizers at atmospheric temperatures. Still more recently, beta-propiolactone (BPL) has been shown to have marked sporicidal, virucidal, and fungicidal activity when it is used in aqueous solution for sterilization of tissues [6] and in the vapor phase for sterilization of enclosed spaces.[7] In spite of its marked activity against all types of micro-organ-

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Summary and Conclusions

With use of the method of intravenous administration of radioactive phosphorus (P^{32}), in an attempt to differentiate in vivo between cutaneous melanoma and clinically similar benign pigmented lesions, we were able to confirm the fact that there is a higher ratio of radioactivity at the tumor site as compared to a contralateral normal skin (control) site for the proved cutaneous melanomas taken "as a group" than there is for other lesions. However, among the 145 skin lesions studied with this method, many false-positive results (20%), in lesions which were not cutaneous melanomas, and many false-negative results (37%), in proved cutaneous melanomas, were obtained.

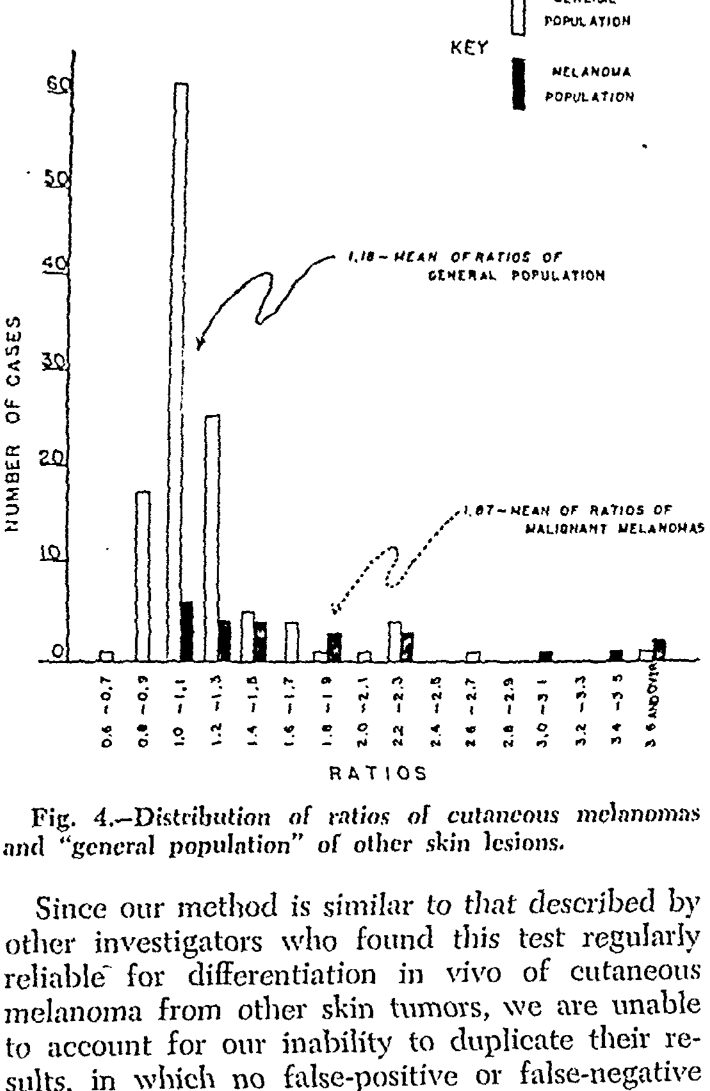

Fig. 4.—*Distribution of ratios of cutaneous melanomas and "general population" of other skin lesions.*

Since our method is similar to that described by other investigators who found this test regularly reliable for differentiation in vivo of cutaneous melanoma from other skin tumors, we are unable to account for our inability to duplicate their results, in which no false-positive or false-negative findings were recorded. On the basis of our findings this test method cannot be depended on in isolated instances to differentiate in vivo between cutaneous melanoma and clinically similar lesions. However, in a large series of cases, if the test information were added to the usual clinical findings, an over-all improved record of correct in vivo diagnoses of melanoma might result.

As pointed out, there are many variables which limit the validity of the results obtained. Among them is the method of measuring the radioactivity within the individual lesions.

The possibility remains that, in the future, a more dependable technique of mensuration, or some modification of the procedure, may be devised to make significant use of the differences in the uptake of radioactive phosphorus (or other radioactive substance) by malignant melanoma compared to other clinically similar cutaneous tumors, resulting in a practical method for making an in vivo diagnosis of superficial melanoma.

40 Journal Square (Dr. Brauer).

Drs. David Lyall and Stephen L. Gumport of the Tumor Clinic, University Hospital, referred several cases for use in this study.

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either in the operating room or in the office by any physician or nurse having the incentive to become familiar with the technique and the simple precautions involved in its use.

Materials and Methods

Test Organisms.—Strains used in prior studies of gaseous sterilization were selected to represent the most resistant species likely to be encountered on surgical instruments. These strains were grown in cooked meat medium (ground beef-heart infusion) freshly prepared according to the method of Holman[13] and containing manganous sulfate, 5×10^{-5} M. After three days' incubation of cultures at 37 C, smears were stained with malachite green (5% aqueous solution) and examined for spore formation. Vegetative forms were killed by pasteurization at 75 C for 60 minutes in a constant temperature water bath. After homogenization in a sterile Waring blendor, serial tenfold dilutions of the uncentrifuged cultures of organisms yielded the following counts: Bacillus subtilis (globigii) strain 9372 (American type culture collection), 1.1×10^{7} viable units per milliliter; Bacillus subtilis (niger) strain 593 (Fort Detrick, Md.), 2.8×10^{8} viable units per milliliter; and Clostridium sporogenes (obtained from the Wilmot Castle Company), 2×10^{7} viable units per milliliter.

Dried spores from these suspensions resisted constant-boiling hydrochloric acid for 30 minutes but not for 60 minutes. Vegetative bacteria were represented by Staphylococcus aureus ATCC 6538 and by a stock strain of pseudomonas.

Carriers.—In most experiments standard suture loops, or paper strips, carrying about 5×10^{5} dried spores per carrier, were used as test objects. In other tests, plastic or metal carriers or instruments were immersed in or swabbed at selected spots with the stock suspension and allowed to dry. Viable vegetative organisms were streaked on blood agar in Petri dishes to be exposed to beta-propiolactone vapor.

Sterility Test Mediums.—For demonstration of viability after exposure to beta-propiolactone, reconstituted fluid thioglycollate medium and freshly prepared cooked meat medium were used. In a sufficient number of experiments, carriers showing no growth were subcultured to cooked meat medium containing 5% horse serum.

All cultures were incubated at 37 C and those showing no growth were kept for 10 days at this temperature. The usual viability controls were included with each experiment and never failed to show growth. Test objects were handled aseptically with flamed hooks or forceps.

Assays were made of liquid beta-propiolactone, but no assays of vapor concentrations were done, other than determination of weight lost from liquid aliquots by vaporization.

Procedure

Objects were exposed to beta-propiolactone either by immersion in an aqueous solution or by exposure to the gaseous phase of the compound. In the former case, sterilization occurs within a few minutes and instruments are ready for use after rinsing. In the latter case, sterilization can begin only after vaporization of a sufficient concentration of beta-propiolactone and of water. Application of the gas laws reveals that the equilibrium concentration of beta-propiolactone in the vapor phase at 25 C and 760 mm. Hg is 13.2 mg. per liter, a concentration about eight times that found sufficient by Hoffman and Warshowsky[7] to kill 90% of spores in two minutes at RH 75-85% and 25-29 C. In order to provide a margin of safety and to speed sterilization, enough liquid beta-propiolactone was used to produce a saturated vapor in the sterilizing chamber.

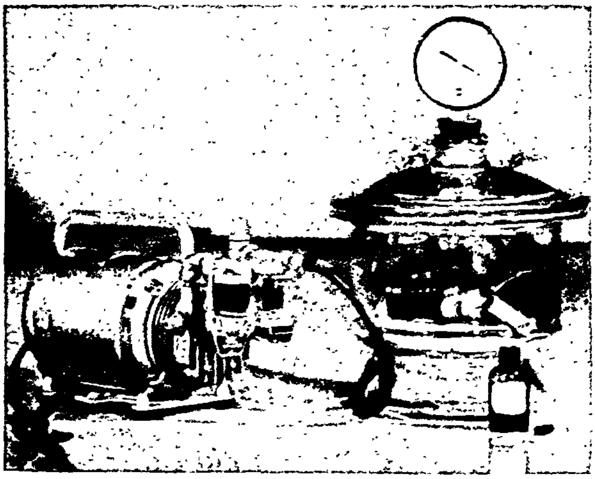

Fig. 3.—Vacuum desiccator, capacity 6.4 liters, attached to vacuum pump and containing optical instruments for *sterilization with beta-propiolactone.*

The following three methods of promoting vaporization of beta-propiolactone were used in these experiments: (*a*) heating the liquid in an air stream; (*b*) atomization; and (*c*) reducing atmospheric pressure by drawing a vacuum. Of these three methods, the first and second can be used in a closed container which need not be hermetically sealed. The third requires an air-tight container.

A sturdy metal box, capacity 12 liters, was used for the experiments in which the liquid was heated in a stainless steel dish over a small resistance coil (50-watt). The coil was connected in series with a small motor-driven fan and the surface of the dish was in the air stream from the fan. Only 0.16 cc. of beta-propiolactone was needed to produce an equilibrium concentration in this container. The temperature in the box reached 27 C (fig. 2).

isms, beta-propiolactone has attracted little attention among surgeons and even among those concerned with sterilizing processes in general. The omission of any reference to it in recent textbooks of sterilization [8] proves this point. The properties of formaldehyde and ethylene oxide are described in these texts. Formaldehyde acts slowly, has an unpleasant odor, and tends to polymerize on surfaces, from which it is difficult to remove by airing. Ethylene oxide is flammable and explosive in air but is harmless to materials and has high penetrating power. Mixed with a suitable inert gas it can be dispensed from an aerosol bomb without danger of explosion. Its adaptation to ophthalmic sterilization has been described by Skeehan and co-workers.[9] To obtain consistent sterilization with ethylene oxide in the hands of ordinary hospital personnel, automatic control of humidity, temperature, gas concentration, and time is required. This entails the purchase of equipment costing about $5,000. Sterilization with ethylene oxide requires several hours under any circumstances.

Although beta-propiolactone is toxic to tissues and penetrates poorly, it is about 25 times more active as a vapor-phase disinfectant than formaldehyde and about 4,000 times more active than ethylene oxide when each substance is used under conditions of maximum effectiveness.[7] Its greater activity permits the use of small quantities of beta-propiolactone for rapid vapor-phase sterilization. Like ethylene oxide, it is easily removed by airing. Unlike ethylene oxide, it is nonflammable in the vapor state and nonexplosive. Beta-propiolactone requires a relative humidity of 75% or higher for rapid kill and is relatively ineffective at lower humidities. These properties led us to explore means of adapting this compound to surgical use for rapid sterilization of delicate instruments and materials in situations in which a surface effect, rather than deep penetration, would suffice.

Beta-propiolactone is a colorless liquid with the formula shown below. The physical properties of beta-propiolactone are as follows [10]: boiling point (760 mm. Hg) 163 C; melting point -33.4 C; density 20/4 C 1.149; vapor pressure (25 C) 3.4 mm. Hg; water solubility 37% (by volume).

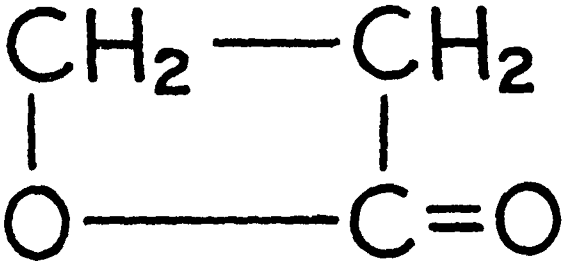

Fig. 1.—Formula of beta-propiolactone.

In aqueous solution, it hydrolyzes to form beta-hydroxypropionic acid. The products of its hydrolysis, which proceed to completion in minutes at an alkaline reaction, are relatively nontoxic and have no microbicidal activity.

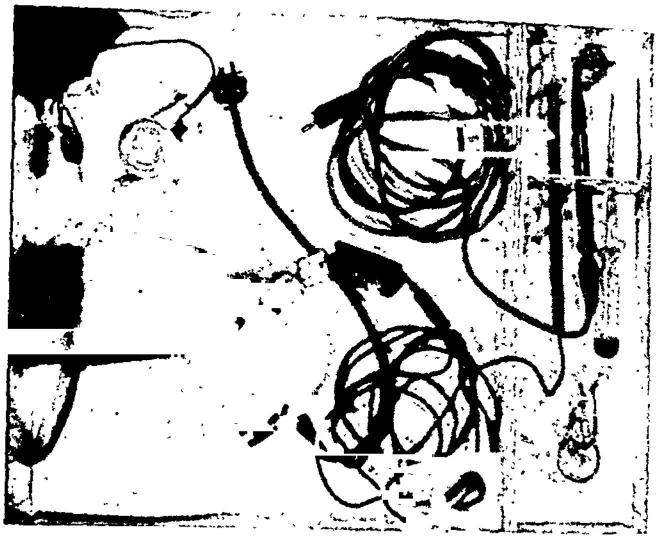

Fig. 2.—Top view of aluminum box, capacity 12 liters, showing instruments for retinal detachment surgery. Fan and heater for beta-propiolactone appear in upper left-hand corner.

The shelf life of purified (99%) or commercial grade (96%) beta-propiolactone is over three years at 4 C.[7] At higher temperatures polymerization proceeds at a rate proportional to the temperature.

Like other potent alkylating agents, beta-propiolactone is toxic to the skin, eyes, and mucous membranes of most species. A single drop of the pure liquid produces irreversible damage to the eye of the rabbit.[11] A 1% solution of beta-propiolactone was deleterious to corneal grafts.[12] Beta-propiolactone produces no immediate or delayed effect on the skin, provided it is washed off without delay. To the time of writing we have not encountered any case of sensitization. We can report from personal experience that inhalation of the vapor produces headache, sweating, tachycardia, "bounding" pulse, epigastric distress, and malaise. However, in view of the minute quantities required for sterilization, beta-propiolactone should present no hazard when carefully handled. If it is accidentally spilled on a surface, flooding this with water or saline solution will initiate hydrolysis and retard vaporization. The acceptance of arterial and bone grafts [6] which have been sterilized with aqueous beta-propiolactone is evidence that no residual toxic effect persists after hydrolysis has taken place.

With these properties in mind we undertook to develop simple sterilizing procedures which would use existing equipment and would not involve the purchase of elaborate and costly devices. As a result of our experience with beta-propiolactone we believe that it can be safely used for sterilization containers kept at 4 C are recommended. For daily use, we have found a 30-cc. bottle with a ground-glass fitted dropper-stopper suitable for dispensing into an atomizer or on a disk of filter paper (Whatman no. 1) the few drops needed for a single sterilization (fig. 5). This bottle should be clearly tagged, labeled, dated, enclosed in another glass container, and stored apart from all medicaments for external or internal use. Beta-propiolactone may be kept at 20 to 25 C for one month but should be replaced from the refrigerated stock bottle at least once a month.

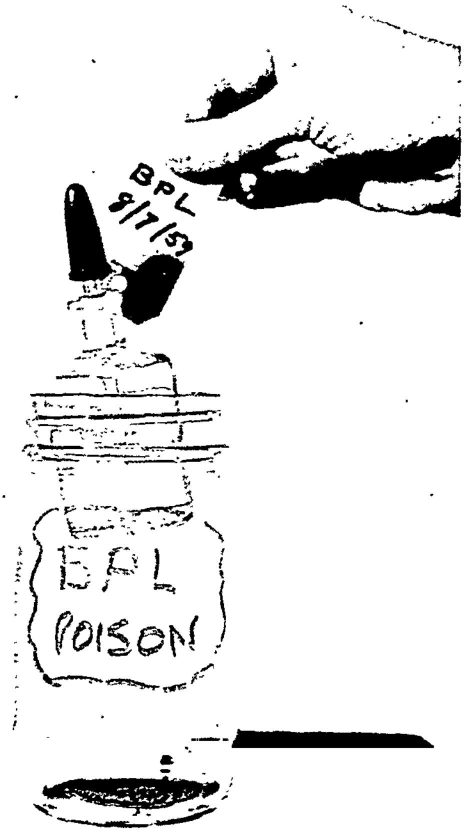

Fig. 5.—Manner of handling beta-propiolactone container by tag attached to bottle neck.

Incorporation of beta-propiolactone into an aerosol bomb, if this could be done without degradation of the active ingredient, might be dangerous if the spray were accidentally released in the direction of some person. We believe that hand-operated devices provide better control for dispersing the small quantities needed.

Removal of beta-propiolactone at the end of the sterilizing cycle presents no problem when small chambers are used. Much of the beta-propiolactone is hydrolyzed in the presence of water vapor and the rest is dissipated almost instantly.

There is practically no limit to the size of objects or spaces which can be sterilized with beta-propiolactone. Anything which can be enclosed in polyethylene film can be sterilized. Metal or plastic wastebaskets can be used as containers for microscopes and closed with polyethylene film. The interior and contents of any room, chamber, or building which can be made reasonably airtight can be sterilized with beta-propiolactone.[7]

The advantages the use of beta-propiolactone for emergency sterilization in the absence of heat and power are obvious. Hospitals should have at least one person who is familiar with the simple techniques described.

200 Beacon St. (16) (Dr. Allen).

This study was supported by the Bacteriology Research Fund of the Massachusetts Eye & Ear Infirmary.

Mrs. Mary Pedulla gave technical assistance and Mr. David Feigenbaum made the figures.

The beta-propiolactone used in these experiments was provided by Surgical Products Division, American Cyanamid Company.

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The second method used to promote vaporization of beta-propiolactone was atomization. Any jet atomizer that produces a sufficiently fine spray would be suitable for this purpose. We found the DeVilbiss 33 pocket atomizer equipped with a DeVilbiss 40 bulb well suited to the small quantities involved. It must be used in the upright position and must therefore be inserted into a hole in the bottom of the chamber. This and similar atomizers can be used to spray beta-propiolactone and water into polyethylene envelopes and stiff containers closed with polyethylene film. Hermetic sealing is not required; however, there should be no circulation of air into the chamber nor appreciable diffusion of beta-propiolactone vapor to the outside during the sterilizing period.

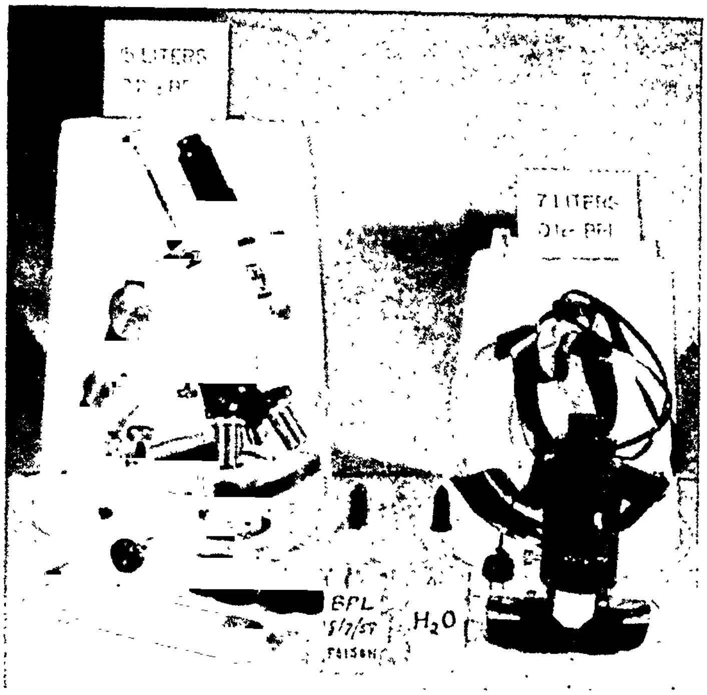

Fig. 4.—Microscope and ophthalmoscope which have been sterilized with beta-propiolactone under inverted plastic wastebaskets.

For the third method of promoting vaporization of liquid beta-propiolactone, we used an ordinary vacuum desiccator, capacity 6.4 liters. This was fitted with a rubber stopper and connected with vacuum tubing to a water aspirator or a small vacuum pump (fig. 3). The time required to draw 29 in. of vacuum was less than five minutes. The amount of liquid beta-propiolactone passing into the vapor phase under these conditions was measured by weighing before and at the end of 30 minutes and was found to be 15 mg. per liter; that is, of the same order as the theoretical concentration.

Several successful experiments were conducted in inverted containers of 1 to 15 liters capacity (fig. 4) in which liquid beta-propiolactone was simply dropped on a pledget of absorbent cotton or a paper towel. A few drops of water were dropped on another part of the paper towel to provide the humidity necessary for the sterilizing action of beta-propiolactone vapor. Because the latter is heavier than air, it should be allowed to diffuse downward around the object to be sterilized.

Results

With volumes of beta-propiolactone and water in excess of those required to produce equilibrium concentrations of vapor in the containers used, test objects and instruments up to the size of the ophthalmic biomicroscope, all heavily contaminated with resistant dry spores or vegetative bacteria, were sterilized at 25 ± 2 C within one hour by each of the four methods described above. More than 20 separate experiments were performed, each involving a number of test objects or instruments. The times required to kill different species are shown in the table.

As is often the case in gaseous sterilization, occasional failures or "skips" occurred in the midst of a series of successful tests. These failures composed less than 2% of all tests and no satisfactory explanation for them is offered.

During the past 14 months, beta-propiolactone vapor has been used by staff nurses for sterilization of ophthalmoscopes, electric cords, and lenses used in ophthalmic surgery at the Massachusetts Eye and Ear Infirmary. No complications have arisen from its use and no instance of postoperative infection has occurred after an operation in which beta-propiolactone was used.

Practical Considerations

The resistant nature and large numbers of bacterial spores destroyed in these tests guarantee the margin of safety necessary for a sterilizing process to be used clinically. The essential reagents in this process are the vapors of water and beta-propiolactone. The effectiveness of the process is predicated on the diffusion or circulation of these vapors throughout the sterilizing chamber in equilibrium concentrations for one hour. Since only surfaces exposed to these vapors will be sterilized, contact between adjacent surfaces in the chamber should be avoided, and objects or materials must be unwrapped.

Sterilization Times at 25±2 C in Equilibrium Concentrations of BPL and Water Vapor

Organism	Form	Minutes
Bacillus subtilis (var. niger)	Dry spores	60
B. subtilis (globigii)	Dry spores	30
Clostridium sporogenes	Dry spores	60
Staphylococcus aureus	Vegetative	10
Pseudomonas aeruginosa	Vegetative	5

Beta-propiolactone must be stored and handled with due consideration for its toxic properties. For prolonged storage of stock quantities, polyethylene

SPECIAL CONTRIBUTION

EFFECTS OF CANCER CHEMOTHERAPEUTIC AGENTS ON THE HUMAN FETUS

Joseph E. Sokal, M.D.
and
Ellen M. Lessmann, M.D., Buffalo

Pregnancy is not a common complication in caner. When it does occur, it often does not affect reatly the treatment of the malignancy, although t may change the prognosis. Occasionally, howver, pregnant women with disseminated malignant lisease are seen as candidates for palliative therapy vith irradiation or chemotherapeutic agents. In uch cases, the presence of the pregnancy may be major factor in determining the therapy to be iven. Although various types of cancer may occur n patients of childbearing age, the subject of caner chemotherapy during pregnancy has been imortant principally in the leukemias and lymhomas, so far, since it is in these diseases that hemotherapeutic agents have been most widely sed. As the use of chemotherapy is extending to ther types of malignancy, however, this problem vill become a more general one.

A major factor in reaching decisions regarding herapy in pregnant women is the possibility of roducing damage to the fetus. Roentgen irradiaion, the principal modality of cancer palliation at resent, is known to be hazardous to the fetus. When contemplated treatment ports include the lower part of the abdomen or pelvis, the risk is rohibitive. When distant areas are treated and the uterus is shielded adequately, the danger of proucing somatic or genetic damage to the fetus is decreased. Under these circumstances, the risks of irradiation therapy are acceptable in selected patients. Little information is available regarding the effects on the human fetus of the major alternative to irradiation, chemotherapy. Since the number of anticancer chemotherapeutic agents and their clinical use is increasing rapidly, it seems desirable to collect information on this point.

The chemotherapeutic agents used in cancer fall into several categories—alkylating agents such as nitrogen mustard, antimetabolites such as 6-mercaptopurine, specific mitosis-blocking agents such as desacetylmethylcolchicine, and various tissue poisons. In general, all of these agents exert their maximum damaging effects on rapidly dividing tissues such as intestinal epithelium, bone marrow, and the reproductive organs. Since a high rate of cell division characterizes the fetus, it would be expected that the fetus would be sensitive to the action of chemotherapeutic agents and that fetal damage would be the rule when effective doses were administered. Such damage should lead to spontaneous abortion, if it were severe enough to make further development of pregnancy impossible, and to congenital abnormalities in the infant, if abortion did not occur.

The effect of various chemotherapeutic agents on the course of pregnancy and on the fetus has been studied extensively in animals. Some representative data from the literature are summarized in table 1. This list is by no means complete and is restricted to compounds of major clinical importance. Most agents have been studied in several laboratories and under various conditions of administration; the results vary somewhat. In addition, there have been many studies in nonmammalian species and in microbial systems. Mutagenic effects among lower organisms have been demonstrated for many cancer chemotherapeutic agents. The following points are apparent from the studies in mammals: 1. Most cancer chemotherapeutic agents can cause fetal death and many can cause congenital malformations in fetuses not killed. 2. The effect on the fetus often depends on the exact times in pregnancy at which the agent is administered. Thus, for example, azaserine caused multiple skeletal abnormalities in rat fetuses when administered between ten and thirteen days of pregnancy but no malformations when administered before or after this period. 3. Although the doses used in many of the animal studies were considerably higher on a weight basis than those used clinically, both fetal death and malformations in living progeny have been induced by some agents (e. g., nitrogen mustard) at doses within the clinical range.

We, like many others, had assumed that administration of chemotherapeutic agents in pregnancy, especially during the first and second trimesters, would be likely to produce abortions or fetal malformations. We have, therefore, in general, avoided their use. However, our recent experience in a patient with chronic myelocytic leukemia treated

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From the Division of Medicine, Roswell Park Memorial Institute.

CLINICAL NOTE

RELATIVE FREQUENCY OF EVISCERATION AFTER LAPAROTOMY IN RECENT YEARS

Ralph Boerne Bettman, M.D.
and
Mathew W. Kobak, M.D., Chicago

The etiology of wound disruption (dehiscence or evisceration) is not known, but postoperative complications such as peritonitis, pneumonia, and wound infections are frequently considered the direct cause. Inasmuch as the advent of the antibiotics has tended to decrease the number of these infections, one might suppose that this decrease would have a definite bearing on the relative incidence of evisceration after laparotomy.

In 1926 one of us (R. B. B.) published a study of the cases of evisceration which had occurred over a previous 10-year period at Michael Reese Hospital.[1] It seemed of interest to restudy the problem in the light of the recent advances in surgery, the "wonder drugs" being among the chief thereof, to see if the relative incidence of evisceration had decreased.

In our first series, covering 1925-1934, we found that there were 32, or 0.43%, cases of evisceration or wound dehiscence after 7,500 major laparotomies.

In our second series, 1947-1956, we found that there were 60, or 0.51%, cases of evisceration or wound dehiscence after 11,694 laparotomies. (In neither series did we include appendectomies performed through muscle-splitting incisions, nor did an evisceration occur after such an operation.)

Thus, the relative number of eviscerations is still small and the difference in relative occurrence is probably of no statistical significance. One thing, however, is certain, and that is that the relative incidence of evisceration, in spite of the progress in surgery, has not diminished.

The mortality after evisceration was 12 patients out of 32, or 37.5%, in our first series, and 12 out of 60, or 20%, in our second series. This is a relative numerical decrease, but, inasmuch as it appeared that in both series the actual cause of death was not the evisceration itself but either the primary disease for which the patient had been operated on or the postoperative complications which seemed to cause the evisceration, this decrease, as far as we can see, has no bearing on the etiology of evisceration.

After a careful and detailed analysis of our studies in our first series we wrote, "The occurrence of evisceration after laparotomy *seemed to* be unpredictable. The uncertainty of this complication is its chief terror."

The analysis and study of our second series (1947-1956) lead us to similar conclusions.

Summary

A careful study of the occurrence of evisceration after laparotomy at Michael Reese Hospital, covering the 10-year period from 1947 to 1956, shows that, since the advent of antibiotics, as well as other advances in surgery, there has been no reduction in the relative frequency of eviscerations. As far as we can see, the occurrence of evisceration is still unpredictable and unaccountable.

A detailed analysis of our report will be published at some future date.

212 Oak Knoll Terrace (*Dr.* Bettman).

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From the Department of Surgery, Michael Reese Hospital.

PROSPECTS FOR THE CONTROL OF GONORRHEA.—It is normally an infection of the promiscuous and is most frequent in the large cities, where immigrants and itinerants congregate and fail to establish stable sexual relationships. The socio-economic factors are complex, but the influence of prostitution and alcohol is clear. The asymptomatic nature of the infection in the female and the persistence of a "reservoir" of gonorrhea in a small but promiscuous section of the female population are the major causes of the failure of our attempts at control. This failure, the rising incidence of gonorrhea, and the threat of penicillin resistance call urgently for research with a biological approach which might, by making possible the immunization of carefully selected groups, eventually lead to the eradication of gonorrhea.—S. M. Laird and R. S. Morton, The Ecology and Control of Gonorrhoea, *British Journal of Venereal Diseases*, September, 1959.

TABLE 2.—*Effects of Cancer Chemotherapeutic Agents in Human Pregnancy*

Case No.	Drug Given	Dosage Mg.	State of Pregnancy at Treatment	Maternal Diseases	Patient's Delivery	Infant follow-up	Primary Reference
1-12	Aminopterin	8-24 over 2 to 5 days	3 to 8 wk.	Various	Spontaneous abortion in 10; Surgical termination in 2	Malformations in 3 fetuses (mothers treated 6 to 8 weeks of pregnancy): hydrocephalus, meningoencephalocele, cleft palate and hairlip; decrease in blood-forming elements, and other microscopic changes	Thiersch, J. B.: Am. J. Obst. & Gynec. 63:1298, 1952
12-23	Aminopterin	Not stated	First trimester	Tuberculosis	Spontaneous abortion in 6; Surgical termination in 5	No details given regarding fetal abnormalities	Thiersch, J. B.: Acta Endocrinol. (suppl. 28) 23:37, 1956
24	Aminopterin	Not stated	First trimester	Tuberculosis	Term delivery	Anencephaly; died at 12 days	Thiersch, J. B.: Acta Endocrinol. (suppl. 28) 23:37, 1956
25	Aminopterin	1 per day for 12 days	3rd mo.	None	Normal	Birth weight 1,289 Gm.; multiple skeletal malformations; deformed ears, mouth; cleft palate; immaturity of ovaries, adrenals, cerebellar cortex; died at 2 days	Warkany, J., and others: A. M. A. J. Dis. Child 97:274, 1959
26	Aminopterin	20 during several weeks	2nd and 3rd mo	None	Normal	Congenital left talipes-equinovarus and multiple skull abnormalities; alive at 4 yrs., marked deformity of head, normal intelligence	Meltzer, H. J.: J. A. M. A. 161:1253, 1956
27	Amethopterin 6-Mercaptopurine	17.5 in 10 days 1.3 Gm. in 27 days	7½ to 8½ mo.	Acute lymphatic leukemia	Cesarean section, 8½ mo.	Normal at 2 yr. of age	Hill, J. M., and Loeb, E.: Personal communication to author
28	Amethopterin 6-Mercaptopurine 6-Mercaptopurine.	20 in 1 mo. 2.7 Gm. in 1 mo. 75 per day	4 to 5 mo. 6 mo. to term	Acute myelogenous leukemia	Normal	Normal at 1½ yr. of age	Hill, J. M., and Loeb, E.: Personal communication to author
29	6-Mercaptopurine and busulfan, alternating courses	Not stated	Throughout pregnancy; exact periods not stated	Chronic myelocytic leukemia	Not described	Small infant (3 lb.), with congenital deformities, died at 2 months; cleft palate, bilateral ocular defects, hypoplasia of thyroid and ovaries; abnormal cell nuclei in many tissues	Diamond, I.: Program, Joint Annual Meeting, Am. Soc. Clin. Path. & Coll. Am. Pathologists, Nov. 1-8, 1958 p. 42
30	Busulfan	0.5 to 4.0 per day	Conception to term	Chronic myelocytic leukemia	Normal, spontaneous	Infant small (4 lb., 6 oz.), otherwise normal; Normal at 3 yr. of age	Izumi, H. M.: J. A. M. A. 161:969, 1956
31	Busulfan	4 to 6 per day for 5 wk. 4 to 6 per day for 2 wk.	2nd-3rd mo. 8th mo.	Chronic myelocytic leukemia	Normal, spontaneous	Normal at 1 yr. of age	Sherman, J. L., and Locke, R. V.: New England J. Med. 259:288, 1958
32	Busulfan	6 per day for 1 mo. 4 per day for 3 wk.	7 mo. to 9 mo.	Chronic myelocytic leukemia	Not described	Normal at 2 yr. of age	Bierman, H. R.: Personal communication to author
33	6-Mercaptopurine	2.5 per kg.	Conception to 7 mo.	Acute leukemia	Premature labor	Infant weighed 3 lb. 3 oz.; died at 2 days; autopsy—normal premature infant	Merskey, C., and Rigal, W.: Lancet 271:1268, 1956
34	6-Mercaptopurine	100 per day	6 mo. to 8 mo.	Acute myeloblastic leukemia	Medical induction, normal	Normal at birth	Schumacher, H. R.: Am. J. Obst. & Gynec. 74:1361, 1957
35	6-Mercaptopurine	25-150 per day	Last 4 mo	Acute myeloblastic leukemia	Normal, spontaneous	Normal at 4 mo.	Rothberg, H. and others: Am. J. M. Sc. 237:194, 1959
36	6-Mercaptopurine Aminopterin 6-Mercaptopurine Desacetylmethylcolchicine 6-Mercaptopurine	75 per day 8 per 6 day 200 per day for 10 days 10 mg. 4 times 50 per day for 2 wks.	Conception to 4th mo. 4th mo. 5th mo. 6th mo. 6th mo.	Acute myeloblastic leukemia	Spontaneous abortion at 6 mo.	Premature infant (1 lb., 9 oz.) lived 19 hr.; no malformations	Rothberg, H. and others: Am. J. M. Sc. 237:194, 1959
37	6-Mercaptopurine	175 per day	3½ mo. to term	Acute myeloblastic leukemia	Normal, spontaneous	Normal at 1 yr. of age	Sandberg, A. A.: Personal communication to author
38	Desacetylmethylcolchicine	2-3 per day	Conception to term	Chronic myelogenous leukemia	Normal	Normal at 2 yr. of age	Zwetschke, O., and Newirtova, R.: Ztschr. ges. inn. Med. 12:974, 1957
39	Desacetylmethylcolchicine	1.5 to 7.5 per day	Conception to term	Chronic myelogenous leukemia	Normal	Normal at birth; iron deficiency anemia at 1 yr.; malnutrition 1-2 yr., died at 2 yr. of postnecrotic cirrhosis of liver (probably due to infectious hepatitis); double left renal artery	Lessman, E. and Sokal, J. E.: Ann. Int. Med. 50:1512, 1959
40	Nitrogen mustard	0.6 per kg.	4 mo.	Hodgkin's disease	Cesarean section, near term	Normal at 8½ yr. of age	Deutschle, K. W., and Wiggins, W. S.: Blood 8:576, 1953

throughout pregnancy with the mitotic poison desacetylmethylcolchicine (Colcemide, Demecolcin) led us to reexamine this subject. We searched the literature for instances of chemotherapy during pregnancy and corresponded with the physicians concerned to obtain follow-up information regarding the fate of the infants. In addition, we inquired of several clinicians with considerable experience in cancer chemotherapy about unpublished cases. Our study was restricted to the classes of chemical agents mentioned above. We have excluded cases treated with ACTH, adrenal steroids, and other hormones whose biological actions have been studied intensively and with which there appears little reason to expect major toxic effects on the fetus. Table 2 shows the information collected through the generous cooperation of many persons. Much to our surprise, we encountered relatively little evidence of fetal damage for most chemotherapeutic agents in clinical use.

TABLE 1.—*Effect of Cancer Chemotherapeutic Agents in Pregnancy—Animal Studies*

Drug Given	Animal*	Dose,* Mg./Kg.	Day of Pregnancy Administered	Fetal Resorption or Abortion, %	Fate of Unresorbed Fetuses	Reference
Nitrogen Mustard	Rat	0.3-0.5	9th-16th	60, when dose given adm. on 11th day; 5-20, other days	Stunted at birth; few abnormalities, 9th and 10th day; 25-50% malformations, 11th to 16th day (encephalocele, various skeletal abnormalities)	Murphy, M. L., and Karnofsky, D. A.: Cancer 9:955, 1956
Triethylenemelamine (TEM)	Rat	0.3-0.5, 2 doses, successive days	4th-5th 7th-8th 11th-12th	80 80-100 16	Rare cranial defects and generalized edema	Thiersch, J. B.: Proc. Soc. Exper. Biol. & Med. 94:36, 1957
Triethylenephosphoramide (TEPA)	Rat	5.0, 2 doses, successive days	4th-5th 7th-8th 11th-12th	80-100 all groups	Stunting, 17-100%; rare cranial malformations	Thiersch, J. B.: Proc. Soc. Exper. Biol. & Med. 94:36, 1957
Chlorambucil	Mouse	10, 20-40, 20	12th-13th 12th-13th 7th	0 0 100	33% dead, at term 100% dead, at term	Didcock, K., and others: Brit. J. Pharmacol. 11:437, 1956
Urethane	Mouse	1,500	3rd-8th 9th-12th *13th-14th*	17-100 0 *20*	Some dead at term; no malformations Mild stunting; skeletal malformations, 30-40% *Some dead at term; no malformations*	Nishimura, H., and Kuginuki, M.: Okajimas Fol. Anat. 31:1, 1958
Urethane	Rat	100, 3 successive days	7th-8th and 9th	A few resorptions	Rare malformations	Tuchmann-Duplessis, H., and Mercier-Parot, L.: Comptes rend. Acad. Sc. 247:152, 1958
Busulfan	Rat	10	14th-16th	0	Normal, except for absence of germinal cells and sterility, in both males and females	Bollag, W.: Schweiz Med. Wchnschr. 84:393, 1954
Desacetylmethylcolchicine	Rat	0.2, 3 successive days	7th-8th and 9th	40	No malformations	Tuchmann-Duplessis, H., and Mercier-Parot, L.: Comptes rend. Acad. Sc. 247:152, 1958
Desacetylmethylcolchicine	Rabbit	1, 2-8	13th-16th 13th-16th	0 100	No data given regarding malformations	Didcock, K., and others: Brit. J. Pharmacol. 11:437, 1956
6-mercaptopurine	Rat	5-30, 2 successive days	4th-5th 7th-8th 12th-13th	44-94, 7th and 8th days 4-12, others	Stunting, 6-50% No malformations	Thiersch, J. B.: Ann. New York Acad. Sc. 60:220, 1954
Aminopterin	Rat	0.2	7th-13th	100, 9th and 10th days; 0-30, others	13% malformations, 11th day; none, others	Murphy, M. L., and Karnofsky, D. A.: Cancer 9:955, 1956
Azaserine	Rat	2.5	7th-18th	50-100, 8th-12th 0-20, other days	60-83% malformations, 10th to 13th days (multiple skeletal defects); none, 7th, 8th, 14th, and 18th days	Murphy, M. L., and Karnofsky, D. A.: Cancer 9:955, 1956
Diazo-oxo-norleucine (DON)	Rat	0.1-1.0	4th-12th	25-100; maximum effect, 8th day	Stunting and malformations; maximum effect 8th day	Thiersch, J. B.: Proc. Soc. Exper. Biol. & Med. 94:33, 1957
5-Fluorouracil	Rat	25-100	9th-14th	Up to 100; most sensitive, 11th day	Various malformations; most sensitive 10th to 12th days	Murphy, M. L., and Karnofsky, D. A.: Personal communication to author

* Agents were administered in single doses, unless otherwise noted.

Review of Clinical Experience

Clear-cut evidence of fetal damage has been demonstrated for the antifolic drug, aminopterin. Thiersch administered this drug to 12 patients with various illnesses, including two with cancer, to induce therapeutic abortion (cases 1 to 12, table 2). Duration of pregnancy ranged from three to eight weeks. Abortion was induced in 10 of these women. In the two failures (treated on the 40th and 54th days of pregnancy) surgical evacuation of the uterus was accomplished. In both of these cases and in one patient treated on the 49th day of pregnancy, who aborted spontaneously, malformations of the fetus were observed. Histological changes were difficult to evaluate, because of the prolonged interval between death of the fetus and examination; however, Thiersch commented on the sparsity of blood-forming elements. In a second series of 12 patients treated by Thiersch (cases 13 to 24), abortion was induced in 6. Five others were surgically

Three pregnant women were treated with nitrogen mustard alone (cases 40, 41, and 42), one with nitrogen mustard and chlorambucil (case 43), one with chlorambucil alone (case 44), three with triethylenemalamine (cases 45, 46, and 47), and three with urethane (cases 48, 49, and 50). In all, normal infants were delivered and no abnormalities have been detected among these children during follow-up observations extending up to nine and one-half years.

Table 3 lists the clinical material according to stage of pregnancy in which chemotherapy was administered. No congenital abnormalities have been seen among children born to women treated only after the first trimester of pregnancy. (Most of these cases had treatment during the second trimester.) Of particular interest are the seven cases treated throughout pregnancy or throughout the first two trimesters. One infant (case 29) was grossly abnormal; one infant (case 30) was small at birth but developed normally and was well at 3 years of age; and one infant (case 39) was normal at birth and at one year but died of cirrhosis of the liver at 2 years of age. Two seriously premature infants (cases 33 and 36) died soon after birth, without malformations. Two children (cases 38 and 48) were alive and well at two and one years of age, respectively.

Table 3.—*Effect of Chemotherapeutic Agents on the Fetus, According to Stage of Pregnancy During Which Treatment was Administered*

	Treated Throughout Pregnancy or First Two Trimesters, No		Treated During First Trimester but Not During Second, No.		Treated During Second Trimester but Not During First, No.		Treated During Third Trimester Only, No.		Total, No.	
Drug	Cases	Major Fetal Abnormality	Cases	Major Fetal Abnormality	Cases	Major Fetal Abnormality	Cases	Major Fetal Abnormality	Cases	Major Fetal Abnormality
Aminopterin, amethopterin	...	...	26	At least 6	2	...	1	...	29	At least 6
Busulfan, 6-mercaptopurine	1	1	...	...	...	...	...	...	1	1
Busulfan	1	...	1	...	...	...	1	...	3	...
6-mercaptopurine	2	...	...		3	...	2	...	7	...
Desacetylmethylcolchicine	2	...	...	...	1	...	...	...	3	...
Nitrogen mustard	...	...	1	...	3	...		...	4	...
Chlorambucil	...	...		...	1	...	1	...	2	...
Triethylenemelamine	...	...	1	...	1	...	1	...	3	...
Urethane	1	...	1	...	1	...	...	...	3	...
Any drug—total cases (duplications eliminated)	7	1	30	At least 6	8	...	5	...	50	At least 7

Comparison of Clinical Experiences and Studies on Animals

There are major discrepancies between the animal studies summarized in table 1 and the clinical data listed in table 2. Most of the chemotherapeutic agents tested in animals induced malformations in surviving fetuses as well as fetal death. This is not true of the data from human beings. Administration of aminopterin produced relatively few fetal abnormalities in rats; it is clearly a dangerous agent for the human fetus. The most sensitive period for the induction of malformation in animals appears to be the middle third of pregnancy. However, we have encountered no reports of malformations among human infants exposed to chemotherapeutic agents after the first trimester of intrauterine life. These discrepancies can be related to the differences in dosage in some cases. More important, however, would appear to be the major differences between man and rodents in the gestational period and time cycle of fetal development. It is also possible that the metabolism of some of the drugs studied may be somewhat different in man and in rats. At any rate, it is evident that experiments made with use of such distant species as the rat have relatively little predictive value in the clinical problem under discussion.

The observations of Thiersch, Warkany and others, and Meltzer constitute unequivocal proof that aminopterin may induce serious fetal malformations as well as abortions, when administered early in pregnancy. The number of experiences with other chemotherapeutic agents are too few to permit definitive conclusions to be drawn. However, the available data suggest that other drugs in common use may not be as dangerous to the fetus as has been generally believed.

Diamond's case is of particular interest. In the clinical material reviewed here, administration of neither busulfan nor 6-mercaptopurine produced major fetal abnormalities when used alone. The multiple and bizarre abnormalities which followed their use in alternating courses suggest a synergistic toxic effect. It is possible that the fetus can adapt to each of these drugs individually but that the metabolic changes required to overcome the toxic effects of one may render the organism more sensitive to the other. Situations of this sort have been well documented experimentally. It may perhaps be desirable, therefore, to restrict chemotherapy during pregnancy to one drug whenever feasible. It should be noted, however, that in table 2 four other cases are included in which more than one drug was used, without any resultant fetal damage. Three of these were treated after the first trimester; the other received only one agent during the first trimester.

TABLE 2.–*Effects of Cancer Chemotherapeutic Agents in Human Pregnancy–Continued*

Case No.	Drug Given	Dosage Mg.	State of Pregnancy at Treatment	Maternal Diseases	Patient's Delivery	Infant follow-up	Primary Reference
41	Nitrogen mustard	0.4 per kg. 0.4 per kg.	4 mo. 5 mo.	Hodgkin's disease	Premature labor, 7 mo.	Normal at 7½ yr. of age	
42	Nitrogen mustard	0.05 per kg.; two doses "3 doses"	1st mo. 7 mo.	Hodgkin's disease	Cesarean section, 8½ months	Normal at 9½ yr. of age	Zoet, A. G.: Northwest Med. 49:373, 1950
43	Chlorambucil	10 per day for 2 wk.	4½ mo.	Hodgkin's disease	Normal	Normal at 2 mo. of age	Smith, R. B., and others: A. M. A. Arch. Int. Med. 102: 777, 1958
	Nitrogen mustard	20 one dose	5 mo.				
	Chlorambucil	10 per day for 1 mo.	5 to 6 mo.				
	Nitrogen mustard	20 twice 20 twice	7th mo. 8th mo.				
44	Chlorambucil	378 in 22 days	7th mo.	Hodgkin's disease	Normal	Normal at 10 mo. of age	Smith, R. B., and others: A. M. A. Arch. Int. Med. 102: 777, 1958
45	Triethylene-melamine (TEM)	"Two courses"	After first trimester	Hodgkin's disease	Normal, spontaneous	Normal at 7 yr. of age	Hennessy, J. P., and Rottino, A.: Am. J. Obst. & Gynec. 63: 756, 1952
46	Triethylene-melamine (TEM)	5 every 3 to 6 days; total –70	5½ mo. to delivery	Subacute lymphatic leukemia	Cesarean section at 8 mo.	Transient slight leukopenia at birth; normal at 5 yr. of age	Bierman, H. R., and others: J. A. M. A. 161:220, 1956
47	Triethylene-melamine (TEM)	16 in 8 days	1st mo.	Hodgkin's disease	Normal	Normal at birth	Smith, R. B., and others: A. M. A. Arch. Int. Med. 102: 777, 1958
48	Urethane	3-4 Gm. per day	Conception to term	Chronic myelogenous leukemia	Normal	Normal at 1 yr. of age	Creskoff, A. J., and others: Blood 3:896, 1948
49	Urethane	3 Gm. per day initially, then 0.3-1 gm./day	3½ mo. to term	Chronic myelogenous leukemia	Normal, spontaneous	Normal at 3½ yr. of age	Imber, I., and Meharg, J. G.: Am. J. Obst. & Gynec. 69:438, 1955
50	Urethane	Not stated	Conception to 3½ mo.	Chronic myelogenous leukemia	Normal	Normal at birth	Gillim, D. L.: Am. J. Obst. and Gynec. 70: 1047, 1955

aborted. Details regarding malformations are not given. One patient went to term and delivered an anencephalic infant who lived 12 days. Warkany and co-workers observed a case in which abortion had been attempted by self-administration of 12 mg. of aminopterin over a 12-day period (case 25). This dose produced maternal toxicity but did not induce abortion. Normal full-term delivery resulted in an infant with multiple severe malformations. Meltzer described a somewhat similar case, in which 20 mg. of aminopterin was ingested over several weeks (case 26). Multiple skull defects and a club foot were observed in the infant. It is of interest, however, that no fetal abnormalities were observed in the three cases of patients receiving antifolic drugs after the first trimester of pregnancy (cases 27, 28, and 36).

Diamond reported major abnormalities in a child born to a patient treated with busulfan (Myleran) and 6-mercaptopurine (case 29). The mother, who had chronic myelocytic leukemia, was treated with alternating courses of these drugs during pregnancy. She gave birth to an undersized infant (3 lb. [1,361 Gm.]) with multiple congenital abnormalities, including microphthalmia, opacity of the corneas, cleft palate, and hypoplasia of the thyroid and ovaries. The infant lived for two and one half months. At autopsy, the most striking histological findings were widespread changes in cell nuclei, with frequent bizarre nuclei observed in many tissues. Izumi reported the birth of a small (4 lb., 6 oz. [1,984 Gm.]) infant to a mother treated throughout pregnancy with busulfan (case 30). This child was otherwise normal and has had an entirely normal postnatal course; she is now 3 years of age. In the two other cases treated with busulfan (cases 31 and 32), the infants were normal. Seven other women treated with 6-mercaptopurine during pregnancy delivered normal premature or full-term infants (cases 27, 28, 33, 34, 35, 36, and 37).

Two women were treated throughout pregnancy with desacetylmethylcolchicine. In both cases, pregnancy and delivery were entirely normal. One child (case 38) developed normally and was entirely well at 2 years of age. The other (case 39) was apparently normal at birth and at one year of age (except for iron deficiency anemia), when our case report was published. Since then, however, she has died of cirrhosis of the liver. During the intervening period, she had had several illnesses and an inadequate diet. Evidence of vitamin A and carotene deficiency was found at autopsy. There was a double renal artery and a large calculus in the left kidney. No abnormalities of cell structure were seen in the liver or other tissues examined. After careful review of the clinical and pathological findings, it was decided by the physicians responsible for the child's care that this case represented a postnecrotic cirrhosis, probably secondary to unrecognized hepatitis.

the question of use of such agents in pregnancy is being raised with increasing frequency. We believe, therefore, that it is worthwhile to attempt to draw some tentative conclusions from the admittedly inadequate data now available. The following points are suggested as a guide to physicians dealing with this problem.

There is considerably more experience with roentgen irradiation of pregnant women than with chemotherapy. Irradiation of distant areas, with adequate shielding of the uterus, is an accepted procedure, although a hazard to the fetus is undoubtedly entailed. Since the information regarding the effects of chemotherapeutic agents on the fetus is so scanty, irradiation should, for the present, remain the preferred palliative treatment for malignancy outside the abdomen and pelvis. On the other hand, since abdominal and pelvic roentgen irradiation have been shown to produce fetal abnormalities and some cancer chemotherapeutic agents have not, chemotherapy with such agents appears preferable for abdominal and pelvic lesions in the pregnant woman, if the fetus is to be preserved.

The use of some cancer chemotherapeutic agents in pregnancy may not be as hazardous as has generally been assumed, especially if treatment is deferred until after the first trimester. Agents which have been used in pregnancy without inducing fetal abnormalities include nitrogen mustard, urethane, 6-mercaptopurine, and chlorambucil. Treatment with triethylenemelamine, in high dosage, produced transient depression of the fetal white blood cell count in one instance but no other abnormalities. Therapy with busulfan may have been responsible for an abnormally small infant in one patient; the child has developed normally and is well at 3 years of age. Administration of desacetylmethylcolchicine may have induced a unilateral renal vascular abnormality in one patient; however, this is a common congenital defect.

Aminopterin, in addition to being a potent abortifacient, can induce major fetal abnormalities when administered during the first trimester of pregnancy. Presumably, this would also be true of amethopterin (Methotrexate).

It may be desirable to restrict use of chemotherapy during pregnancy to one agent, whenever feasible, because of the possibility that combinations of drugs may produce more fetal damage than one drug alone. Multiple severe fetal abnormalities were induced by alternating courses of busulfan and 6-mercaptopurine; administration of neither drug alone has induced important fetal damage in the cases reviewed. Furthermore, subsequent evaluation of the effect of chemotherapy on the infant will be much easier if only one drug has been used.

Data from animal experiments can serve only as a rough guide in situations in which no human experience exists. Such data may not be directly applicable to human beings. The outcome of all cases of pregnancy in which cancer chemotherapeutic agents have been administered should be reported. Only the accumulation of detailed information regarding infants born to such patients can provide a sound guide for the proper management of this difficult though uncommon clinical problem. In particular, long-term follow-up reports on such children are needed.

Summary

The effects of cancer chemotherapeutic agents on the human fetus have been reviewed. Follow-up information has been assembled on children born to women treated with various cytotoxic agents during pregnancy; the oldest child traced is now 10 years of age. Aminopterin, in addition to being a potent abortifacient, can induce major fetal abnormalities when administered during the first trimester of pregnancy. Other drugs in clinical use have proved far less toxic for the fetus than would have been anticipated from theoretical considerations or animal experiments. Busulfan and 6-mercaptopurine, administered in alternating courses throughout pregnancy, produced multiple severe fetal abnormalities, although neither drug alone produced major fetal damage. No reports of important fetal abnormalities have been encountered in cases in which chemotherapeutic drugs were used only after the first trimester of pregnancy.

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An important consideration is the stage of pregnancy at which chemotherapeutic agents are administered. Animal studies indicate that chemotherapeutic agents are most damaging to the fetus during the middle third of pregnancy. Although the data reviewed here do not permit final decision on this point, this is most probably not true for the human. Antifolic drugs produced fetal abnormalities in at least six patients treated during the first trimester but in neither of the two treated during the second trimester. It is known that the human fetus is most susceptible to teratogenic agents such as rubella virus and roentgen irradiation during the first trimester, and it is probable that this is also the case for cancer chemotherapeutic drugs. At any rate, no fetal abnormalities have been reported in the 13 cases in which maternal chemotherapy was administered only after the first trimester. Eight of these were treated during the second trimester.

It is likely that, as in animals, the induction of malformations of the human fetus requires administration of chemotherapeutic agents at specific stages of gestation. Furthermore, individual drugs may act at different, sharply defined periods of fetal development. Thus, for example, the absence of deformities in the four infants born to mothers treated with nitrogen mustard may be due simply to good fortune in the timing of therapy. Of particular interest, therefore, are the patients receiving chemotherapy continuously for all or almost all of the first two trimesters. In such cases, favorable results constitute positive evidence against drug toxicity for the fetus. Seven cases fall into this category. In two patients treated principally with 6-mercaptopurine, one treated with urethane, and one treated with desacetylmethylcolchicine, no fetal abnormality was detected. In the second patient who was treated with desacetylmethylcolchicine, fetal damage may possibly have occurred. However, the hepatic cirrhosis was attributed to postnatal disease and the double renal vessels may have been coincidental; the latter is a common congenital abnormality. The condition of the patient who was treated with busulfan is difficult to evaluate. Although the infant was abnormally small at birth, it was otherwise normal and has developed normally.

The resistance of the human fetus to potent cytotoxic agents is rather puzzling. One would expect that antimetabolites and alkylating agents would be damaging to a rapidly growing embryo. Fetal blood-forming tissues, in particular, should be easily damaged by cancer chemotherapeutic agents. However, the experience reviewed here provides no evidence to support this hypothesis. Only one instance of depression of the infant's blood count at birth was described (case 46). In this case, the mother had been treated with large doses of triethylenemelamine for 11 weeks prior to and during delivery. The infant, delivered by elective cesarean section one month before term, had transient slight leukopenia. Although the mother had severe thrombocytopenia and moderately severe anemia at the time of delivery, the infant's platelet count and hematocrit value were normal. It would appear either that there may be a partial block in the transport of some agents across the placental barrier or that fetal tissues are less easily damaged by these agents than are maternal blood-forming elements.

Comment

A major concern of the physicians who treat pregnant women with disseminated cancer is the possibility that use of a suitable therapeutic agent for the maternal disease may result in the birth of a living infant with serious congenital abnormalities. Such an event would be a tragic blow to a family already suffering under the burden of the impending death of the mother. The possibility that a therapeutic agent may induce abortion is perhaps a less serious consideration. We have focused our attention on the problem of congenital abnormalities rather than on the question of abortion induced by chemotherapeutic agents. The latter would be difficult to evaluate, except for aminopterin, which is clearly a potent abortifacient. The incidence of spontaneous abortion is increased in patients with leukemia [1] or active Hodgkin's disease.[2] In view of the limited clinical data available, it would be impossible to decide at this time whether agents other than aminopterin increase the frequency of abortion among such women.

Obviously, the number of cases reviewed here is small, and the follow-up of infants born to treated mothers is relatively short. It would be unwise to state that maternal chemotherapy did not produce fetal damage, just because the children were apparently normal during the first decade. Defects in some tissues might not become manifest until much later. Bollag's experiments with busulfan-treated rats furnish an example of this. The young were apparently normal at and soon after birth but later proved to have sexual hormone deficiencies and were sterile. No children born of mothers who had received chemotherapy have yet reached the age of puberty. It is possible that abnormalities of some endocrine organs or of germinal tissues, not now apparent, may become evident later. Finally, it has been shown that doses of roentgen irradiation which do not produce any detectable short-term effects may lead to premature death and senile changes in animals.[3] If similar results are produced by some of the cancer chemotherapeutic agents (whose biological effects often resemble those of roentgen irradiation), this will not become apparent for another 20 or 30 years.

It will be many years, therefore, before a definitive evaluation of the effects of chemotherapeutic agents on the human fetus can be made. However, more than a dozen affiliated local "research clubs." Its official publication is *Clinical Research*, devoted largely to the programs and abstracts of its national and regional meetings.

Concentration of young talent in medical research in Atlantic City beginning on May 1 will not be equaled until the Annual Meeting of the same associations the next year. The American Society for Clinical Investigation will convene after the Federation meetings. The Association of American Physicians will be the last large group to assemble. It is safe to state that the future of medical research in America rests largely with those who attend the Atlantic City meetings during the four-day conclave.

Perusal of the Federation program reveals the volume of investigation to be discussed. It is almost overwhelming for any one person to comprehend the depth or the magnitude of the problems investigated. A few typical subjects on which papers are to be presented at the Federation meeting are "The Nature of Elevated Peripheral Resistance in Hypertension"; "The Effect of a Protein Free Diet on Experimental Nephritis"; "Renal Glomerular and Vascular Lesions During the Course of Diabetes Mellitus"; and "Differences in Amount of Illness and in Signs Believed Prognostic of Atherosclerosis in Two Groups of Young Men."

But medical research was not always as gargantuan. America placed a poor third to England and Central Europe in such endeavors in the first quarter century of the 1800's. Pierre Louis, the leader of the French school, strongly supported the scientific approach to the classification of disease. The physician performed the dual role of clinician and pathologist. The fame of the European schools spread abroad and prompted the publishing of journals in America that reported European observations. Thus the *Eclectic Repertory*, founded in 1819 in Philadelphia, changed its name to *The Journal of Foreign Medical Science*. It concentrated on communications from England and France during the next decade. By the 1830's, several physicians were returning to the United States after postgraduate study under Louis. Shryock[1] speculated that, "Had it not been for the untimely death of James Jackson, the younger, full-time medical research might have been introduced into America at that time." According to Samuel Jackson in 1832, "The essential trouble was the commercialism of the age which led to a worship of wealth and accorded little recognition to intellectual achievements. Physicians, caught up in this environment, depended for prestige as well as for income on a successful practice. Even wealthy men, therefore, would not take time off for original work. As a remedy, the Philadelphian beseeched his students to attempt research in their first lean years, ere the shades of money-making closed about them."

A little more than a century later, the clinical investigator who comes to Atlantic City finds financial support and security to pursue research scarcely dreamed of as recently as 20 years ago. The investigator is free to permit insatiable curiosity to lead him wherever it will. He is free to reveal his findings and to express his conclusions—but not without discussion from his associates. The communications presented at the Federated meetings are noteworthy in this respect. The polemic that follows most presentations may be astute, perceptive, analytical, but not disparaging. This is as it should be, not only in Atlantic City, May 1, 1960, but throughout the world.

A TIME UNREMEMBERED

Scarcely a physician in practice remembers a time when, as he glanced down the cover of each issue of The Journal, he did not see a description of a new book from the W. B. Saunders Company. The Saunders box on the cover of this issue is unique. It contains a farewell message after 60 years and after more than 3,000 consecutive appearances. The position will be relinquished so that we may present a more attractive face to our readers. Although this small window through which the progress of medical publishing has been evident is now gone, it is not forgotten. A medical landmark does not vanish without some nostalgia—and so it is with us.

Some of us may remember when Saunders had an obvious half-page on The Journal. This brought to the attention of the practicing physician such excellent tomes as Labat's "Anesthesia," Abt's "Pediatrics," Beckman's "Treatment," and Bickham's "Operative Surgery." Each one of the 23 editions of Dorland's Illustrated Medical Dictionary was announced on the front of The Journal.

Medical publishing is the handmaiden of medical education, in spite of other mediums that may claim this honor. Both have marched forward together, and many of the titles of Saunders' books which have appeared on the front cover constitute a composite of America's best medical writing for more than a half-century. The first announcements of the publication of the following excellent volumes appeared on the cover of The Journal: Arey's "Developmental Anatomy," DeLee's "Principles and Practice of Obstetrics," Ewing's "Neoplastic Diseases," Garrison's "History of Medicine," Jordan's "Bacteriology," Maximow's and Bloom's "Histology," Ranson's "Neuro-anatomy," and Sollman's "Pharmacology." This was as much a matter of pride to us as it was for the House of Saunders, because a prime concern of the American Medical Association has been the sound as well as imaginative advancement of medical education. There is little doubt that the titles and authors of these books would have done honor and added prestige to the front cover of any medical journal. They were books that looked forward and extended the frontiers of medical knowledge. Among them were books that took courage to write and courage to publish as well as courage to allocate unlimited hours for preparation of the manuscript.

THE JOURNAL
OF THE AMERICAN MEDICAL ASSOCIATION

Editor . . . . JOHN H. TALBOTT, M.D.
Editor Emeritus . . JOHNSON F. HAMMOND, M.D.
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News Editor . . . . CHARLES CHAPMAN
Feature Writer . . . . RICHARD P. PRATT

THE MIAMI BEACH SCIENTIFIC PROGRAM

THE Annual Meeting of the American Medical Association in Miami Beach, Fla., June 13 through 17, will present to physicians many new features and trends in medicine for the first time. It is especially appropriate that these new presentations be made at Miami Beach, since this is the A. M. A.'s first Annual Meeting in the state of Florida.

The air-conditioned Miami Beach Auditorium and Exhibition Hall will house more than 290 scientific exhibits as well as outstanding scientific lecture programs to be presented by the Section on General Surgery and the Section on Obstetrics and Gynecology. Color television, which will originate at the Mount Sinai Hospital in Miami Beach, will bring a full week's program, featuring some of the outstanding topics of the day, to the stage of the Auditorium.

A selected group of motion pictures, featuring five première films, will be presented in the Exhibition Hall. This program will also include two motion picture symposiums, one on colitis and one on polyps and cancer of the large intestine. Many of the authors of these films will be present for the symposiums and panel discussions.

The general scientific lectures on Monday afternoon, June 13, which will be presented in the Grand Ballroom of the Fontainebleau Hotel, will be an up to the minute discussion on nutrition with a lecture on "The Two-Carbon Chain at the Crossroads of Medicine," leading a series of studies covering daily problems facing those who understand the importance of nutrition in illness. The second general scientific meeting on Tuesday, June 14, will feature a joint effort of six Sections of the Scientific Assembly to solve common problems in "The Evaluation and Preparation of the Patient for Anesthesia and Surgery."

The other Section programs will be presented in the Fontainebleau and Eden Roc Hotels, while the Section on Dermatology will hold its meeting in the Di Lido Hotel. A list of all Section meeting places appears elsewhere in this issue of THE JOURNAL.

The Scientific Exhibit will highlight the research being conducted at a number of research centers throughout America and, in addition, will cover those subjects that can be incorporated in a doctor's busy daily practice. The competition for space in the Scientific Exhibit, the keenest in many years, demonstrates the high regard the practicing physician and the medical scientist have for the value of the A. M. A. Scientific Exhibit.

You will find the author or a demonstrator at each exhibit booth to assist you in finding the answers to your questions or to discuss specific problems with you. The special exhibits which have been so popular through the years will be expanded to include an exhibit featuring a Clinical Forum on Body Fluid Disturbances. This forum will proceed on a schedule so that if one does not wish to attend the whole course of lectures, he may attend one particular phase or lecture on the subject. To afford as large a group as possible the opportunity to attend this two-day exhibit, it will be repeated on Wednesday and Thursday, June 15 and 16.

The other special exhibits on Fractures, Fresh Tissue Pathology, and Pulmonary Function will be expanded to include new material. The annual Physical Examinations for Physicians will include audiometric tests and intraocular tension examinations.

MAY DAY

A fortnight from now, May Day will be celebrated in a number of countries throughout the world. The Union of Soviet Socialist Republics can be expected to parade selected examples of new weapons to awe the outsider. May 1 in West Germany will be an enlightened Labor Day for a prosperous, thriving, industrial people. May Day heralds the blossoming of spring flowers in northern United States, while specifically in Atlantic City May 1, 1960, is the first of several days when medical research is supreme.

The American Federation for Clinical Research will be in the spotlight the first day. The Federation, once identified as "The Young Men's Christian Society" in honor of its founder Henry Christian (better known now as the Young, Young Turks), will sponsor six programs on as many special areas of research interest, running concurrently.

The Federation has an inclusive membership policy. To be an Active Member, it is only necessary that the applicant be younger than 41 years and produce evidence of completion and publication of a meritorious investigation in clinical medicine or allied sciences. About one-third of the Federation's 3,500 members, having passed the age of 41, are senior members now. Their function is to stimulate and encourage young men to pursue careers in clinical investigation. The parent organization sponsors four active regional groups and

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1. Shryock, R. H.: "Medicine and Society in America, 1660-1860," New York University Press, 1960.

WELCOME TO MIAMI BEACH

In a little over one-half a century Miami, on the east coast of Florida (which has at various times flown the French, Spanish, British, and United States flags) has literally gone from rags to riches—from a tiny isolated fishing village to a wealthy resort city. In the spring of 1896, when the first train puffed its way into Miami, even Henry F. Flagler, the entrepreneur who built the railroad, voiced doubts about the future of this tropical wilderness.

The first semblance of civilization in the Biscayne Bay area was the establishment in 1836 of Fort Dallas at the mouth of the Miami River. Built in an effort to control the warlike Seminole Indians, Fort Dallas was abandoned by the government several years later. But a few members of the garrison, having succumbed to the magic spell of a balmy climate and subtropical scenery, remained behind.

Seven days after the last section of track was laid the first passenger train arrived, and there followed a kaleidoscopic century of booms, epidemics, building of homes and hotels, fires, real estate development, growth of educational institutions, depressions, wartime changes, and tourist activity. Industry flocked to the area in the 1950's. Airlines clamored for routes in and out of Miami, as the Miami International Airport became the second busiest in the nation. A new 26 million dollar passenger terminal opened in 1958, close on the heels of the inauguration of jet service between Miami and New York.

Because the average summer temperature in Miami is 79 F, Miami is gaining in popularity as a year-around resort city. The pollen-free, southeasterly trade winds keep the days comfortably warm and the evenings cool enough to permit sleeping under a blanket. The city has 380 hotels, many of which have swimming pools. Among the many tourist attractions is the 800-year-old Spanish Monastery purchased by William Randolph Hearst in 1925, brought to this country, and reassembled here in 1954. Others include the Seaquarium, Children's Zoo, Monkey Jungle, Wax Museum, Snake Farm, and Seminole Indian Village. The Hialeah Race Track is not far away, and there is always the ocean with its miles of beach and opportunities for deep sea fishing. Glass bottomed boats take visitors over the offshore reefs for a close-up view of the underwater life that abounds in colorful profusion in these subtropical waters. Brightly colored fish and plants may be seen clearly in these natural sea gardens. Those who drive their cars to Miami will be well advised to make the trip to the Everglades National Park and the beautiful trip along the Florida Keys.

Pool, cabanas, and recreation area of Hotel Americana—headquarters hotel.

It would be remiss of us, too, if at this time we did not recall the service messages that appeared from time to time in the Saunders box. There were messages that urged physicians to attend the annual A. M. A. Meetings and to support the Clinical Sessions. Some may remember that during World War II physicians were asked to cooperate with drives for saving scrap materials. Notices such as these constitute only one among the many items that have served to nourish the warm and friendly feeling between the medical profession and the Saunders Company for more than a half-century. Through all these years, the front cover notices have been calm and unhurried. No extravagant claim, except the occasional intimation of universal interest in a work of highly specialized knowledge, has betrayed fundamental faith in a worthy product. We hope to continue to see the Saunders book announcements on the inside pages of The Journal for many years to come.

This, then, is a farewell message to an old friend in a tweed jacket. This friendship was never more manifest than at the time that Saunders agreed to relinquish this desirable spot. The conference that led to this momentous decision lasted less than two hours. It was one of the first major suggestions of the new regimen in the editorial division.

Giving up the front cover was done wryly but graciously. The cover will be permitted a little more of that most valued of earthly possessions—elbow room. Possibly we should confess sympathy for Thoreau, who preferred to sit on a pumpkin and have it alone than to be crowded on a velvet cushion.

A PLEA FOR THE UNCONCEIVED

We live in an era of anxiety and confusion. The advances of science seem to have outrun our common sense. Ironically, while one group of scientists assure us of massive genetic death from radiation fall-out, another group are as insistent that we are so fertile that the planet will have standing room only. Obviously both cannot be correct. Providence, which gave man mind and spirit, fortunately has permitted him to meet each challenge of fate since the day of the cave dweller. *Necessitas est mater inventionis.*

In the era of the planned family one is apt to forget the heartache of the involuntarily childless couple. Mother's day awards go to the prolific sister. As often as not the less fertile sister is suspected of voluntary abstinence from nature's greatest privilege. Robert Frost, the sage of New England, recently remarked, however, that though science may enable man to control his own evolution, the test tube will never replace passionate preference. Strong psychosomatic influences are important, but fertility is basically biological.

Most infertile couples are only partially infertile as a complete study of both partners will demonstrate. There is a better than even chance fo success if studies are commenced after a year o involuntary childlessness. Youth is the talisman o successful maternity; so is the timing of the trys between the sperm and the egg.

Accordingly, the description of Doyle, on page 1744, in this issue of The Journal, of a simple inexpensive procedure which will enable a woman to know daily the extent of her period of maximum fertility offers new hope to the childless woman and to the overburdened cardiac or tuberculous mother alike. Positive and negative family planning for responsible parenthood is now possible without moral scruples. Childbirth without fear is now joined by a new ally—conception without fear Natural child spacing has arrived. Recent advances in veterinary physiology from South Africa are assuringly confirmatory. A glucose tide occurs in the uterine fluids of cattle, sows, and ewes—and even in race horses.

It is refreshing that the authors insist on medical supervision of this new procedure. The determination of basal waking temperature patterns still has an important place in estimating the qualitative hormonal efficiency of the corpus luteum, though its accuracy as an indicator of ovulation time has long since been suspect to those who, like the present authors, have tested it against the microscopic evidence of the endometrium and the corpus luteum. Nor can one neglect semen analysis, tubal insufflation, and Sims-Huhner tests. Recent observations by MacLeod have confirmed a long held suspicion. The sperms are found with maximal motility within the uterus within 90 seconds after coitus. The aspiration of the glucose-laden uterine estuary as postulated by Hartman is thus confirmed. The role of antispasmodic and tranquilizing drugs in relieving psychogenic-uterotubal spasm is rapidly relieving the necessity for hypnotism or deep psychoanalysis, both of which are effective but not without psychological hazards to the marriage itself.

Riva has recently indicated the importance of culdoscopy in a study in which one-third of a series of infertile women revealed unsuspected disease. The transvaginal surgical exploration in which no hand or gauze is introduced into the pelvis gains new disciples with the advent of better detergents in skin preparations. Yet, only a minority of patients require surgery—for fibroids, polyps, ovarian tumors, endometriosis, or tuberculosis.

The surgical investigator must be a bridge tender —channeling knowledge from biological science to the patient's bedside and back again. He traces his origin from both ends of the bridge.

The unconceived has no tragic face to challenge the heart of men. Too little have the biologically minded surgeons begged for the necessary funds to finance research to aid the wanted child. Let us hope it is not yet too late.

THE MIAMI BEACH MEETING

AMERICAN MEDICAL ASSOCIATION, ONE HUNDRED NINTH ANNUAL MEETING

MIAMI BEACH, JUNE 13-17, 1960

OFFICIAL CALL

To the Officers and Members of the
American Medical Association

The 109th Annual Meeting of the American Medical Association will be held in Miami Beach, June 13-17, 1960.

House of Delegates: The House of Delegates will convene at 10 a. m., Monday, June 13, in the Ballroom of the Americana Hotel. The representation of the constituent associations in the House for the 1960 Annual Meeting is as follows:

Alabama	2
Alaska	1
Arizona	1
Arkansas	2
California	17
Colorado	3
Connecticut	3
Delaware	1
District of Columbia	2
Florida	4
Georgia	3
Hawaii	1
Idaho	1
Illinois	11
Indiana	5
Iowa	3
Isthmian Canal Zone	1
Kansas	2
Kentucky	2
Louisiana	2
Maine	1
Maryland	3
Massachusetts	6
Michigan	7
Minnesota	4
Mississippi	2
Missouri	4
Montana	1
Nebraska	2
Nevada	1
New Hampshire	1
New Jersey	6
New Mexico	1
New York	17
North Carolina	3
North Dakota	1
Ohio	9
Oklahoma	2
Oregon	2
Pennsylvania	12
Puerto Rico	1
Rhode Island	1
South Carolina	2
South Dakota	1
Tennessee	3
Texas	8
Utah	1
Vermont	1
Virgin Islands	1
Virginia	3
Washington	3
West Virginia	2
Wisconsin	4
Wyoming	1

The scientific sections of the American Medical Association, the Medical Corps of the Army, the Medical Corps of the Navy, the Medical Corps of the Air Force, the Public Health Service, and the Veterans Administration are entitled to one delegate each.

Scientific Assembly: The Scientific Assembly of the Association will open with the General Scientific Meetings to be held in the Ballroom of the Fontainebleau Hotel on Monday, June 13, at 1:30 p. m., and on Tuesday, June 14, at 9 a. m.

Sections of the Scientific Assembly will meet Tuesday, June 14, beginning at 2 p.m.; all day Wednesday and Thursday, June 15 and 16; and on Friday morning, June 17. Information on specific times and places will be found on page 1784 of this issue of THE JOURNAL.

Scientific Exhibits: The scientific exhibits will be housed in the Miami Beach Exhibition Hall and Auditorium; the exhibits will open at 8:30 a. m. on Monday, June 13, and close at noon on Friday, June 17.

Industrial Exhibits: The industrial exhibits will be housed in the Miami Beach Exhibition Hall and Auditorium; the exhibits will open at 8:30 a. m. on Monday, June 13, and close at noon on Friday, June 17.

Registration: The Registration Bureau will be located near the main entrance of the Miami Beach Exhibition Hall; it will be open as follows:

Sunday, June 12, 12 noon to 4 p. m.
Monday, June 13, 8 a. m. to 5:30 p. m.
Tuesday, June 14, 8:30 a. m. to 5:30 p. m.
Wednesday, June 15, 8:30 a. m. to 5:30 p. m.
Thursday, June 16, 8:30 a. m. to 5:30 p. m.
Friday, June 17, 8:30 a. m. to 12 noon

Inaugural Meeting: The Inaugural Meeting at which the President will be installed will be held on Tuesday, June 14, at 8:30 p. m., in the Grand Ballroom of the Fontainebleau Hotel.

Louis M. Orr, President
Norman A. Welch, Speaker, House of Delegates
R. M. McKeown, Secretary-Treasurer

HOUSE OF DELEGATES

MEMBERS OF THE HOUSE OF DELEGATES

A Preliminary Roster of the Legislative Body of the American Medical Association

The list of members of the House of Delegates for the session is incomplete. Following is a list of the holdover members of the House of Delegates and of the newly elected members who have been reported to the Executive Vice President in time to be included:

DELEGATES FROM CONSTITUENT ASSOCIATIONS

ALABAMA

M. Vaun Adams, Mobile
E. Bryce Robinson Jr., Fairfield

ALASKA

Milo H. Fritz, Anchorage

ARIZONA

Jesse D. Hamer, Phoenix

ARKANSAS

James M. Kolb, Clarksville
Sam G. Jameson, El Dorado

CALIFORNIA

E. Vincent Askey, Los Angeles
Cyril J. Atwood, Oakland
Warren L. Bostick, San Rafael
Donald Cass, Los Angeles
Donald A. Charnock, Los Angeles
James E. Feldmayer, Exeter
Paul D. Foster, Los Angeles
Leopold H. Fraser, Richmond
Henry Gibbons III, San Francisco
Eugene F. Hoffman, Los Angeles
R. Stanley Kneeshaw, San Jose
J. Lafe Ludwig, Los Angeles
Frank A. McDonald, Sacramento
Sam J. McClendon, San Diego
J. Burris M. Price, Santa Ana
H. Milton Van Dyke, Long Beach
Dwight L. Wilbur, San Francisco

COLORADO

Irvin E. Hendryson, Denver
Everett H. Munro,
Grand Junction
Kenneth C. Sawyer, Denver

CONNECTICUT

James R. Cullen, Hartford
John N. Gallivan, East Hartford
Norman H. Gardner,
East Hampton

DELAWARE

H. Thomas McGuire, New Castle

DISTRICT OF COLUMBIA

Ralph M. Caulk, Washington
Raymond T. Holden, Washington

FLORIDA

Reuben B. Chrisman Jr.,
Coral Gables
Burns A. Dobbins Jr.,
Ft. Lauderdale
Francis T. Holland, Tallahassee
Meredith Mallory, Orlando

GEORGIA

Eustace A. Allen, Atlanta
J. W. Chambers, LaGrange
Henry H. Tift, Macon

HAWAII

Harry L. Arnold Jr., Honolulu

IDAHO

Raymond L. White, Boise

ILLINOIS

Walter C. Bornemeier, Chicago
Harlan English, Danville
Frank H. Fowler, Chicago
Arthur F. Goodyear, Decatur
Percy E. Hopkins, Chicago
B. E. Montgomery, Harrisburg
Joseph T. O'Neill, Ottawa
H. Kenneth Scatliff, Chicago
Carl Steinhoff, Chicago
Leo P. A. Sweeney, Chicago
C. Paul White, Kewanee

INDIANA

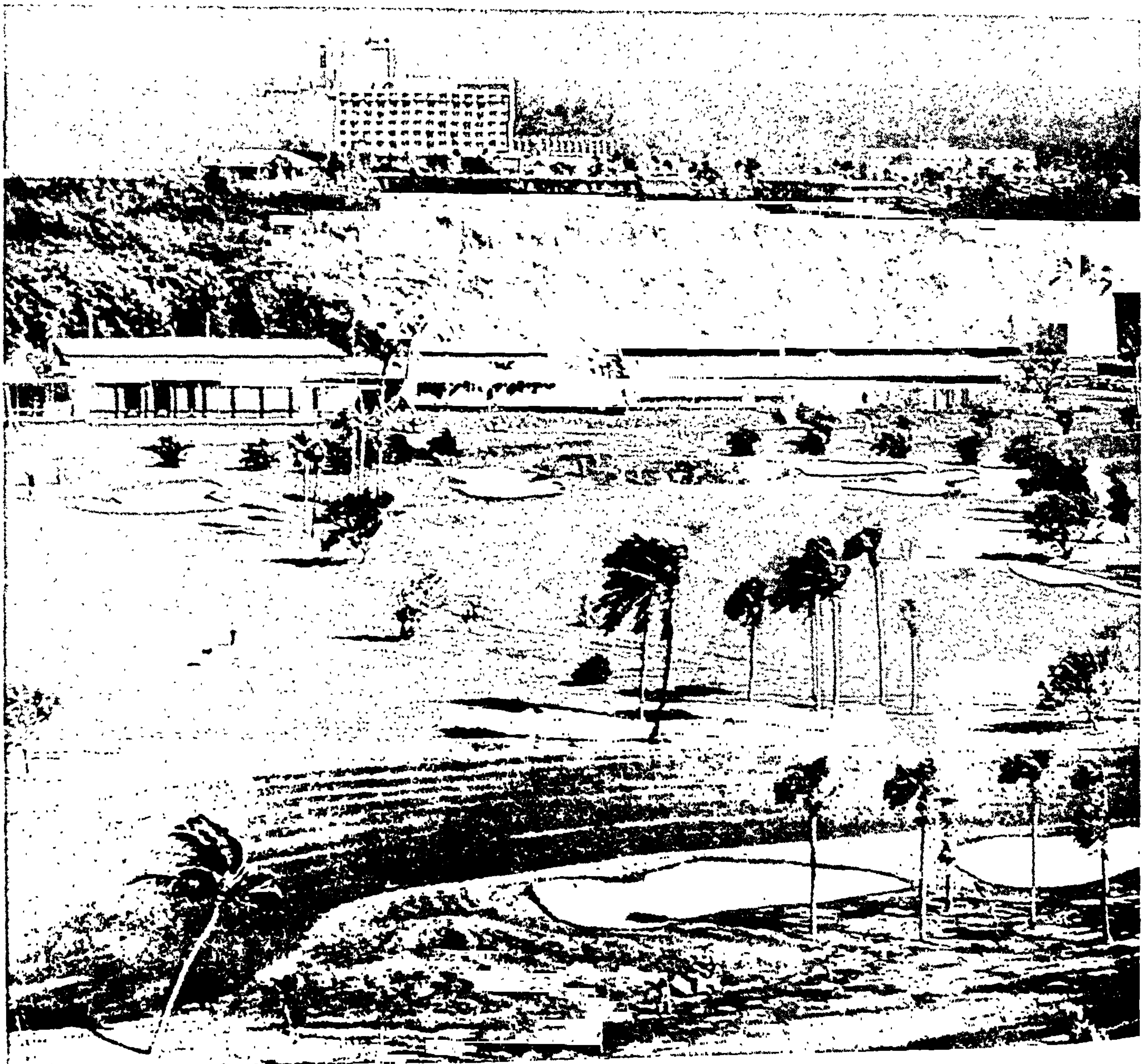
Eli S. Jones, Hammond
Francis L. Land, Fort Wayne
Harold C. Ochsner, Indianapolis
Wendell C. Stover, Boonville
Gordon B. Wilder, Anderson

GOLF TOURNAMENT

Golf minded physicians who plan to attend the annual meeting of the American Medical Association will be offered an opportunity to play one of the finest 18-hole championship courses in the country. The 44th annual tournament will be held at the Diplomat Country Club, Hollywood, Fla. The outstanding facilities of this club are located on a 400-acre site fronting on the Atlantic Ocean. *Tee off* has been scheduled for 8:00 a. m. through 2:00 p. m. on Monday, June 13. This will give participants the opportunity to start early and finish by lunch time, to play the first nine before lunch and finish after the noon meal, or to complete the entire 18 holes after lunch.

In the late afternoon professional exhibitions will be scheduled to give pointers and help to members of the American Medical Golf Association after they complete their play. The cocktail hour will be from 6:00 p. m. to 7:00 p. m. and will be followed by the annual banquet and meeting. Prizes for tournament play will be awarded after the banquet.

Members of the American Medical Association who do not hold membership in the American Medical Golf Association should contact Dr. John A. Growdon, 1324 Professional Bldg., Kansas City, Mo., to secure an application form. The AMGA features a *lifetime membership* to A. M. A. members on the payment of a membership fee of $3. There are no annual dues to the association, but members pay tournament fees for *those* annual events that *they participate* in. A limited number of rooms are available at the Diplomat Hotel for those members desiring to stay at the tournament site for the duration of the A. M. A. meeting.



Golf course at Diplomat Country Club, Hollywood, Fla.

NOTICE TO DELEGATES

The House of Delegates at the 1960 Miami Beach Meeting will convene at 10 a. m., Monday, June 13, in the Ballroom of the Americana Hotel.

The Reference Committee on Credentials will meet at the following times and places:

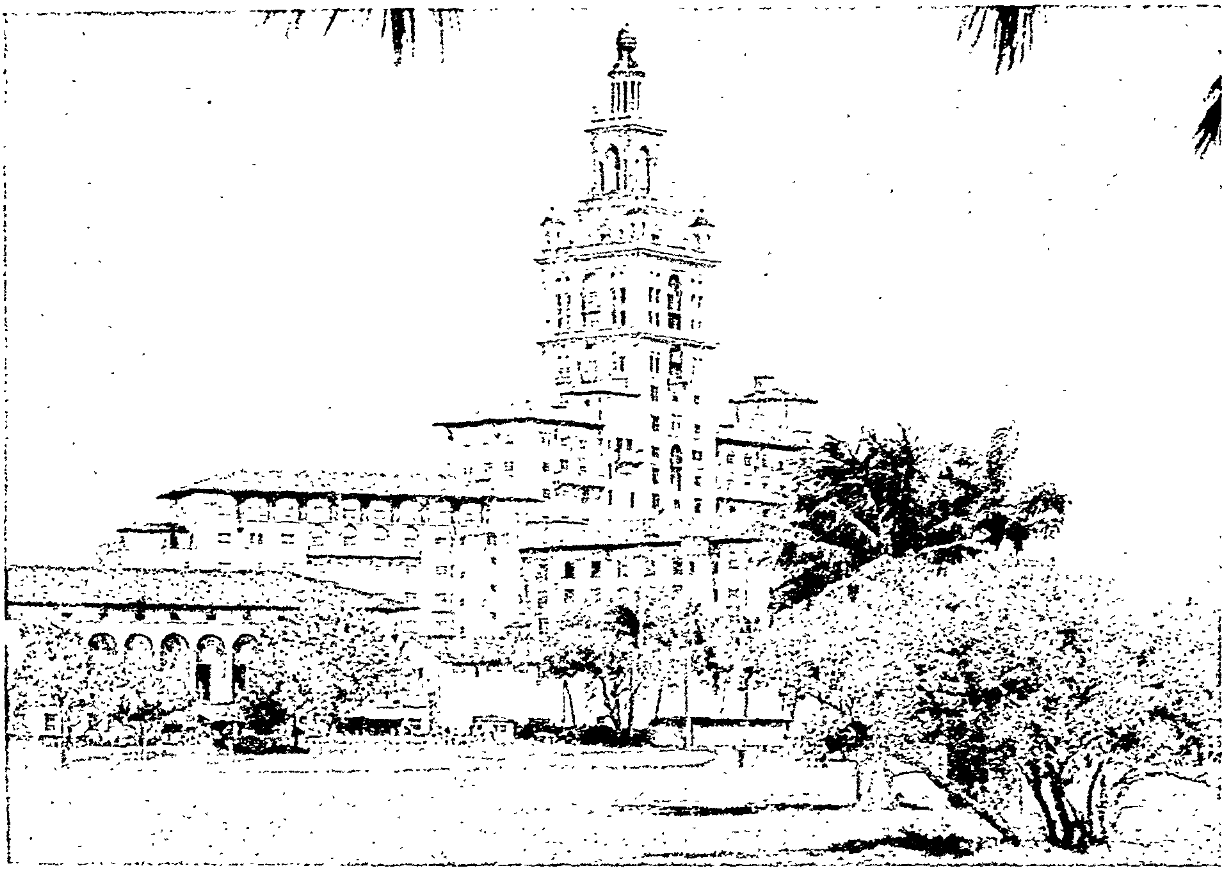
Sunday, June 12, 3 p. m. to 6 p. m.—Ballroom
Monday, June 13, 8 a. m. to 10 a. m.—Medallion Room

The Committee will also meet preceding each subsequent meeting of the House of Delegates. It will be noted that the Reference Committee on Credentials is to meet for a few hours on Sunday afternoon, June 12; it is hoped that as many delegates as possible will take advantage of this opportunity to present their credentials.

Each delegate should present to the committee properly executed credentials which have been signed by the president or secretary of the constituent association, by the chairman or Secretary of a Section of the Scientific Assembly, or by the surgeon general or chief medical director of the government service represented. Alternate delegates presenting credentials should see that the delegates whose places they are to take have signed the alternate authorization.

Meeting rooms have been provided for the use of Reference Committees of the House of Delegates. Reference Committee meetings must be held at the time and in the room assignd so that any who are interested in referred matters may appear before the committees.

The A. M. A. Headquarters Office, the center for the preparation of official reports, resolutions and motions, will be located in the Ballroom of the Americana Hotel. According to the Bylaws resolutions must be in the hands of the Speaker or submitted to the A. M. A. Headquarters Office (Miami Beach) not later than noon of the day preceding the opening meeting of the House, i. e., Sunday, June 12. If feasible, however, resolutions should be sent to the Executive Vice-president of the Association in Chicago by June 1 in order that they may be processed and duplicated in advance of the meeting.



Coral Gables Biltmore golf course and VA Hospital adjoining the University of Miami Medical School.

REGISTRATION

Physicians' Registration will be located near the main entrance of the Miami Beach Exhibition Hall: it will be open as follows:

Sunday, June 12, 12 noon to 4 p. m.
Monday, June 13, 8 a. m. to 5:30 p. m.
Tuesday, June 14, 8:30 a. m. to 5:30 p. m.
Wednesday, June 15, 8:30 a. m. to 5:30 p. m.
Thursday, June 16, 8:30 a. m. to 5:30 p. m.
Friday, June 17, 8:30 a. m. to 12 noon

Who May Register

Members—Active, Affiliate, Associate, Service, Honorary—and invited guests may take part in the work of the sections and may register for attendance at meetings.

IOWA

Francis C. Coleman, Des Moines
Robert N. Larimer, Sioux City
Donovan F. Ward, Dubuque

ISTHMIAN CANAL ZONE

KANSAS

George F. Gsell, Wichita
L. R. Pyle, Topeka

KENTUCKY

Robert C. Long, Louisville
W. Vinson Pierce, Covington

LOUISIANA

Philip H. Jones, New Orleans
Ralph R. Riggs, Shreveport

MAINE

Philip P. Thompson Jr., Portland

MARYLAND

Robert vanLieu Campbell,
Hagerstown
J. Sheldon Eastland, Baltimore
George H. Yeager, Baltimore

MASSACHUSETTS

Lawrence R. Dame, Greenfield
Philip S. Foisie, Boston
Charles G. Hayden, Boston
Henry F. Howe, Cohasset
Nicholas S. Scarcello, Worcester
Norman A. Welch, Boston

MICHIGAN

Wyman D. Barrett, Detroit
John S. DeTar, Milan
William A. Hyland, Grand Rapids
O. J. Johnson, Bay City
Robert L. Novy, Detroit
Clarence I. Owen, Detroit
G. W. Slagle, Battle Creek

MINNESOTA

Orwood J. Campbell, Minneapolis
R. L. J. Kennedy, Rochester
A. E. Ritt, St. Paul
A. O. Swenson, Duluth

MISSISSIPPI

John P. Culpepper Jr.,
Hattiesburg
John F. Lucas, Greenwood

MISSOURI

Durward G. Hall, Springfield
Richard H. Kiene, Kansas City
Arthur W. Neilson, St. Louis
H. E. Petersen, St. Joseph

MONTANA

Paul J. Gans, Lewistown

NEBRASKA

Earl F. Leininger, McCook
Joseph D. McCarthy, Omaha

NEVADA

Wesley W. Hall, Reno

NEW HAMPSHIRE

Louis C. Theobald, Exeter

NEW JERSEY

C. Byron Blaisdell, Asbury Park
William F. Costello, Dover
Aldrich C. Crowe, Ocean City
J. Wallace Hurff, Newark
L. Samuel Sica, Trenton
Elmer P. Weigel, Plainfield

NEW MEXICO

Earl L. Malone, Roswell

NEW YORK

Walter P. Anderton, New York
Renato J. Azzari, Bronx
James M. Blake, Schenectady
Peter J. DiNatale, Batavia
Gerald D. Dorman, New York
Henry I. Fineberg, Jamaica
John M. [illegible], Glen Cove
Leo E. [illegible]
Thurm[illegible]
James [illegible]
John F. Kelley, Utica
Joseph A. Lane, Rochester
John C. McClintock, Albany
Norman S. Moore, Ithaca
Peter M. Murray, New York
William B. Rawls, New York
Carlton E. Wertz, Buffalo

NORTH CAROLINA

Elias S. Faison, Charlotte
Millard D. Hill, Raleigh
Charles F. Strosnider, Goldsboro

NORTH DAKOTA

Willard A. Wright, Williston

OHIO

John H. Budd, Cleveland
Charles L. *Hudson, Cleveland*
Carl A. Lincke, Carrollton
Richard L. Meiling, Columbus
Carll S. Mundy, Toledo
Charles A. Sebastian, Cincinnati
C. C. Sherburne, Columbus
George A. Woodhouse,
Pleasant Hill
Herbert B. Wright, Cleveland

OKLAHOMA

Wilkie D. Hoover, Tulsa
Malcolm E. Phelps, El Reno

OREGON

E. G. Chuinard, Portland
Archie O. Pitman, Hillsboro

PENNSYLVANIA

Daniel H. Bee, Indiana
William F. Brennan, Pittsburgh
Gilson Colby Engel, Philadelphia
Harold B. Gardner, Harrisburg
M. Louise C. Gloeckner
Conshohocken
W. Benson Harer, Upper Darby
Samuel B. Hadden, Philadelphia
Louis W. Jones, Wilkes Barre
George S. Klump, Williamsport
Edward Lyon Jr., Williamsport
Thomas W. McCreary, Rochester
Elmer G. Shelley, North East

PUERTO RICO

Luis R. Guzman-Lopez, San Juan

RHODE ISLAND

Charles J. Ashworth, Providence

SOUTH CAROLINA

George D. Johnson, Spartanburg
William Weston Jr., Columbia

SOUTH DAKOTA

Arthur A. Lampert, Rapid City

TENNESSEE

William C. Chaney, Memphis
Charles C. Smeltzer, Knoxville
Daugh W. Smith, Nashville

TEXAS

G. W. Cleveland, *Austin*
Joseph B. Copeland, San Antonio
John K. Glen, Houston
Milford O. Rouse, Dallas
Troy A. Shafer, Harlingen
James C. Terrell, Stephenville
Truman C. Terrell, Fort Worth
James H. Wooten Jr., Columbus

UTAH

Kenneth B. Castleton,
Salt Lake City

VERMONT

James P. Hammond, Bennington

VIRGIN ISLANDS

VIRGINIA

Vincent W. Archer,
Charlottesville
W. Linwood Ball, Richmond
W. Allen Barker, Roanoke

WASHINGTON

M. Shelby Jared, Seattle
Jesse W. Read, Tacoma
A. G. Young, Wenatchee

WEST VIRGINIA

Charles A. Hoffman, Huntington
Frank J. Holroyd, Princeton

WISCONSIN

E. L. Bernhart, Milwaukee
R. E. Galasinski, Milwaukee
A. A. Quisling, Madison
L. O. Simenstad, Osceola

WYOMING

Albert T. Sudman, Green River

DELEGATES FROM THE SECTIONS AND GOVERNMENT SERVICES

ANESTHESIOLOGY

Joseph H. Failing, Los Angeles

DERMATOLOGY

Winfred A. Showman,
Tulsa, Okla.

DISEASES OF THE CHEST

J. Winthrop Peabody Sr.,
Washington, D. C.

EXPERIMENTAL MEDICINE AND THERAPEUTICS

Harry F. Dowling, Chicago

GASTROENTEROLOGY AND PROCTOLOGY

Stuart T. Ross, Garden City, N.Y.

GENERAL PRACTICE

Lester D. Bibler, Indianapolis

GENERAL SURGERY

R. Russell Best, Omaha

INTERNAL MEDICINE

Charles T. Stone Sr.,
Galveston, Texas

LARYNGOLOGY, OTOLOGY AND RHINOLOGY

Gordon F. Harkness,
Davenport, Iowa

MILITARY MEDICINE

Alphonse McMahon,
St. Louis, Mo.

NERVOUS AND MENTAL DISEASES

Francis M. Forster, Madison, Wis.

OBSTETRICS AND GYNECOLOGY

Ralph E. Campbell,
Madison, Wis.

OPHTHALMOLOGY

Ralph O. Rychener,
Memphis, Tenn.

ORTHOPEDIC SURGERY

Edward L. Compere, Chicago

PATHOLOGY AND PHYSIOLOGY

Lall G. Montgomery, Muncie, Ind.

PEDIATRICS

Walter B. Stewart, Atlantic City

PHYSICAL MEDICINE

Walter J. Zeiter, Cleveland

PREVENTIVE MEDICINE

R. T. Johnstone, Los Angeles

RADIOLOGY

Eugene P. Pendergrass,
Philadelphia

UROLOGY

Jay J. Crane, Los Angeles

UNITED STATES AIR FORCE

UNITED STATES ARMY

Leonard D. Heaton

UNITED STATES NAVY

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PUBLIC HEALTH SERVICE

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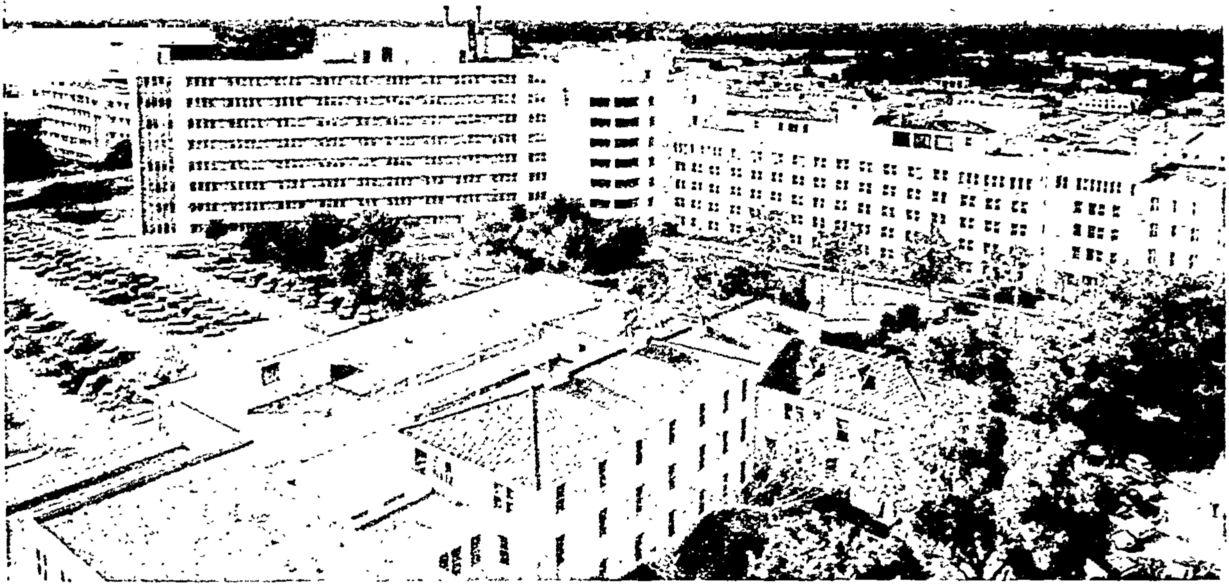
The General Officers, Trustees, Executive Vice-President, Assistant Executive Vice-President, Editor and two Delegates from the Student American Medical Association are ex officio Members of the House of Delegates.

MIAMI BEACH HOTEL RESERVATIONS

If hotel accommodations have not yet been secured, it is suggested that the application form which may be found on advertising page 336 of this issue of The Journal be filled in and sent directly to the A. M. A. Annual Meeting Housing Bureau, P. O. Box 1511, Miami Beach, Fla. Applications for hotel accommodations should not be sent to the American Medical Association office in Chicago as it delays receipt of the application by the A. M. A. Housing Bureau and its subsequent processing.

INAUGURAL CEREMONY

Dr. E. Vincent Askey, Los Angeles, will be inaugurated as President of the American Medical Association at special ceremonies Tuesday evening, June 14, in the Ballroom of the Fontainebleau Hotel. The Inaugural Ceremony is open to physicians and their families, exhibitors, and guests.



Jackson Memorial Hospital, University of Miami.

ENTERTAINMENT

President's Reception and Ball

The President of the Association will be honored after the Inaugural Ceremony with a reception and ball, to be held Tuesday evening, June 14, in the Ballroom of the Fontainebleau Hotel. Members of the Association and their guests are invited to attend.

Physicians Art Exhibit

The 23rd Annual Exhibition of Art Works by members of the American Physicians Art Association will be held in conjunction with the A. M. A. Annual Meeting in the Miami Beach Auditorium, between June 13 and 17. For further information contact Kurt F. Falkson, M.D., 7 E. 78th St., New York 21.

Luncheons, Dinners and Meetings of Alumni, Fraternal and Allied Medical Associations

Alumni Association of Rush Medical College, Luncheon, Tuesday, June 14, 12:30 p. m., Delano Hotel, Zodiac Room. Tickets at $3.50 available from Alumni Office, 1758 W. Harrison St., Chicago, or A. M. A. Alumni Registration Desk at Meeting.

American Association of Public Health Physicians, Informal Discussion, Sunday evening, June 12, through Thursday, June 16, Deauville Hotel.

American Rheumatism Association, Seminar, June 11th, 1:45 p.m., Diplomat Hotel. Registration is $15. For further information write to American Rheumatism Association, Seminar Committee, 1206 Huntington Medical Bldg., Miami 32, Fla.

American Society of Internal Medicine, meeting with the President of the Society, Sunday afternoon and evening, June 12, Discussion, Wednesday, June 15, 7:30 p.m., Americana Hotel.

American Therapeutic Society, Reception and Cocktail Party, Thursday, June 9, 8:00 p. m.; Reception and Banquet, Saturday, June 11, 7:30 p. m., Barcelona Hotel.

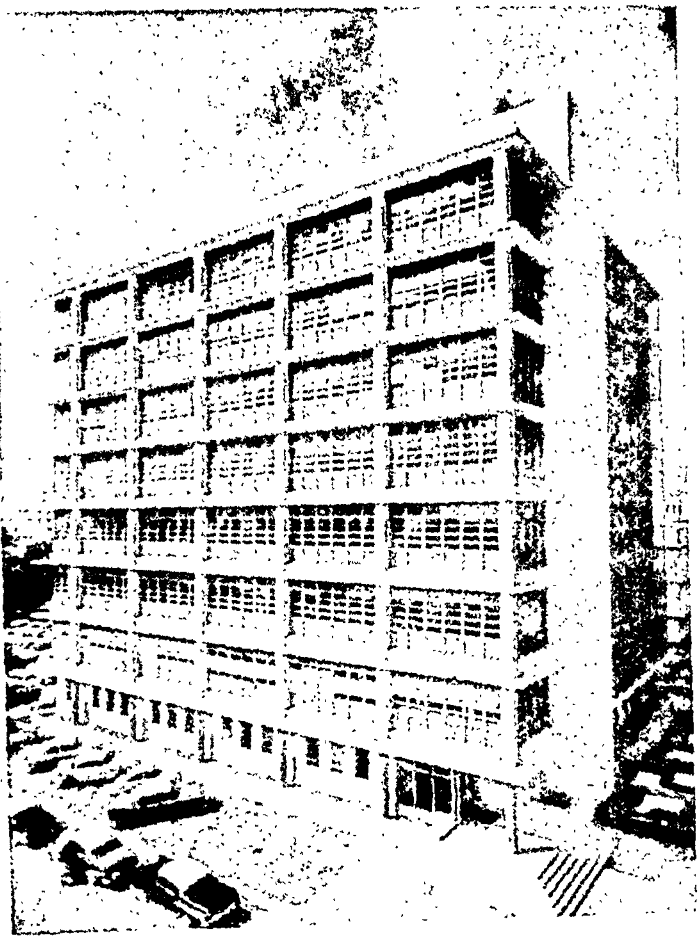
American Medical Women's Association, June 10, 11 and 12, Carillon Hotel, Gold Room, Baroque Room.

Association for Research in Ophthalmology, diLido Hotel.

Chicago Medical School Alumni Association, Dinner, Wednesday, June 15, 6:00 p. m., Saxony Hotel, Veranda Room. Tickets at $6.50 available from Chicago Medical School Alumni Association, 710 S. Wolcott Ave., Chicago 12.

Creighton University Medical Alumni, Luncheon, Tuesday, June 14, 11:30 a. m., Delano Hotel, Fala Room. Tickets at $3 available from the A. M. A. Alumni Registration Desk at Meeting.

Residents, interns, medical students, Student A. M. A. members, and registered nurses will be given registration cards at a designated window. These should be filled in and presented at the window indicated, together with their professional identification or a card or letter signed by the dean of the medical school they attend.



Medical research building on new campus of University of Miami Medical School.

Register Early

Members living in the Miami Beach area, as well as all other physicians who are in Miami Beach on Sunday, are urged to register as early as possible. Registration is open on Sunday, June 12 between 12 noon and 4 p. m.

Suggestions That Will Facilitate Registration

Members who present Advance Registration Cards can be registered with little or no delay, if the name of their hotel or local address, the number of guests they wish to register, and a check mark opposite the Scientific Section in which they wish to be enrolled are filled in prior to registering at the Exhibition Hall.

The completed card may be presented at the windows marked "Advance Registration" at which time the member will receive a badge and a copy of the Official Program. To receive an Advance Registration Card, the coupon on advertising page 338 of this issue of The Journal may be completed and sent to the American Medical Association, 535 N. Dearborn St., Chicago 10, before May 20, 1960.

Members without Advance Registration Cards will find blank cards to be completed on tables in the registration area at the Exhibition Hall. The completed card is to be presented, together with an American Medical Association Membership Pocket Card, at the space indicated. The Pocket Card will be returned and a badge and a copy of the Official Program will be furnished.

Registration at Americana Hotel

General Officers of the American Medical Association, members of the House of Delegates, alternate delegates, and the president, president-elect, and constitutional secretary of the constituent medical associations may register at the Americana Hotel. Advance registration facilities will be set up in the A. M. A. Headquarters Office in the Ballroom; it will be open as follows:

Saturday, June 11, 4 p. m. to 8 p. m.
Sunday, June 12, 9 a. m. to 8 p. m.

On Monday, June 13, registration facilities will be set up in the Medallion Room; it will be open from 8 a. m. to 11 a. m.

Delegates are urged to register early so that all members of the House of Delegates may be seated in time for the opening session of the House, which will convene at 10 a. m., Monday, June 13.

Medical Society Executives Registration

Staff members of state, territorial, and county medical societies, editors of state medical journals and county society bulletins, and staff members of national medical society organizations of medical interest may register in the A. M. A. Headquarters Office in the Ballroom of the Americana Hotel; advance registration facilities will be open as follows:

Saturday, June 11, 4 p. m. to 8 p. m.
Sunday, June 12, 9 a. m. to 8 p. m.

On Monday, June 13, registration facilities will be set up in the Medallion Room; it will be open from 8 a. m. to 11 a. m.

See advertising page 336 for hotel registration coupon, room rates schedule, and map of Miami Beach.

FOR PHYSICIANS ONLY

Physicians and special guests only will be admitted to view the Scientific and Industrial Exhibits at the Miami Beach Exhibition Hall at the following specified tmes:

Tuesday, June 14—8:30 a. m. to 12 noon
Wednesday, June 15—8:30 a. m. to 12 noon
Thursday, June 16—8:30 a. m. to 12 noon

This includes the Television and Motion Picture Programs which are a part of the Scientific Exhibit.

CREDIT FOR ATTENDING MEETING

Military Services

Point credit will be given to active and reserve officers of the Air Force, Army, and Navy who attend the Miami Beach Meeting. Proper credit cards may be obtained at the desk outside the meeting room for the Section on Military Medicine at the Fontainebleau Hotel on Tuesday afternoon, June 14, and at the Eden Roc Hotel on Wednesday and Thursday mornings, June 15 and 16.

General Practice

The American Academy of General Practice will giv credit in Category I to those members of the Academy wh attend the Miami Beach Meeting. Proper credit cards ma be obtained at the desk outside the meeting room for th Section on General Practice at the Fontainebleau Hotel o Tuesday afternoon, June 14, and Wednesday, Thursday, an Friday mornings, June 15, 16, and 17.

Alumni Association, New York Medical College, Luncheon, Tuesday, June 14. Time and place to be announced.

American Physicians Fellowship, Inc., Monday, June 13, 8:30 p. m., Delano Hotel, Annual Assembly Meeting.

Boston University Medical School Alumni Association, Dinner, Wednesday, June 15, 7:00 p. m., Shore Club Hotel, Hawaiian Room. Tickets available at the A. M. A. Alumni Registration Desk at Meeting.

Christian Medical Society, Banquet, Wednesday, June 15, 6:30 p. m. Tickets available from the Christian Medical Society Exhibit. Place to be announced.

The Graduates' Society of McGill University, Luncheon, Tuesday, June 14, 12:30 p. m., Hotel diLido, Card Room. Tickets at $3.50 available from the Graduates' Society of McGill University, 3618 University St., Montreal 2, Quebec, Canada.

Phi Chi Medical Fraternity, Luncheon, Wednesday, June 15, 12:15 p. m., Delano Hotel, Zodiac Room, Tickets available from the A. M. A. Alumni Registration Desk at Meeting.

Tufts Medical Alumni Association, Cocktail Party, Wednesday, June 15, 6:00 p. m., Eden Roc Hotel. No admission charge.

University of Louisville, Dinner and Cocktail Party, Wednesday, June 15, 6:00 p. m. Tickets available from the Alumni Office University of Louisville, and from the A. M. A. Alumni Registration Desk at Meeting.

University of Wisconsin Medical Alumni Association, Luncheon, Tuesday, June 14, 12:00 noon, Sea Isle Hotel. Tickets at $5 available from the Medical Alumni Office, 418 N. Randall, Madison, Wis.

Western Reserve University Medical Alumni Association, Luncheon, Tuesday, June 14, 12:00 noon. diLido Hotel. Tickets at $3 available from the Alumni Office, Western Reserve University School of Medicine, 2109 Adelbert Rd., Cleveland 6, and at A. M. A. Alumni Registration Desk at Meeting.

Northwestern University Alumni Association, Medical Division, Luncheon, Tuesday, June 14, 12:15 p. m., Roney-Plaza Hotel, Imperial Room. Tickets at $3.50 available from the Northwestern University Medical Alumni Office, 303 E. Chicago Ave., Chicago 11, or the A. M. A. Alumni Registration Desk at Meeting.

National Federation of Catholic Physicians' Guilds, Reception-Hospitality Hour, Wednesday, June 15, 6:00 p. m., Seville Hotel. Tickets on request available from the National Federation of Catholic Physicians' Guilds, 1438 S. Grand Blvd., St. Louis 4, Mo.

Phi Lambda Kappa Fraternity, Dinner, Tuesday, June 14, 7:00 p. m., Barcelona Hotel. Tickets at $7.50 available from Charles Rosenfeld, M.D., 1500 Coral Way, Miami, Fla.

Society for Investigative Dermatology, Inc., Dinner, diLido Hotel.

Phi Delta Epsilon Fraternity, Open House, Wednesday, June 15, 9:00 p. m. to Midnight, Delano Hotel, Outdoor Patio. No charge or tickets.

Spanish monastery. (City of Miami News Bureau photograph.)

University of Kansas Medical Alumni Association, Reception, Wednesday, June 15, 5:00 p. m., Hotel Shelborne, Starlight Room. Tickets at $2.50 available from the A. M. A. Alumni Registration Desk at Meeting.

University of Maryland Alumni, Reception and Dinner, Wednesday, June 15, 6:30 p. m., Roney-Plaza Hotel, Ivy Terrace and Imperial Room. Tickets at $7.50 available from the University of Maryland Alumni, University of Maryland, Lombard and Greene Streets, Baltimore 1, Md., or the A. M. A. Alumni Registration Desk at Meeting.

University of Nebraska College of Medicine Alumni Association, Luncheon, Tuesday, June 14, 12:30 p. m., Hotel Shelborne, Starlight Room. Tickets at $5 available from the University of Nebraska College of Medicine Alumni Association, 42nd and Dewey, Omaha 5.

University of Pennsylvania Medical Alumni Society, Reception and Dinner, Wednesday, June 15, Hotel Fontainebleau.

Columbia University, College of Physicians and Surgeons, Alumni Association, Dinner, Wednesday, June 15. Further details to be announced. Tickets available from Alumni Office, 630 W. 168th St., New York 32.

Duke Medical Alumni Association, Dinner, Wednesday, June 15, 6:30 p. m., The Embers. Tickets at $10, available from T. L. Peele, M.D., Box 3811, Duke Hospital, Durham, N. C.

Fifty Year Club of Physicians. Registration of names of interested physicians at A. M. A. Registration Desk at Meeting.

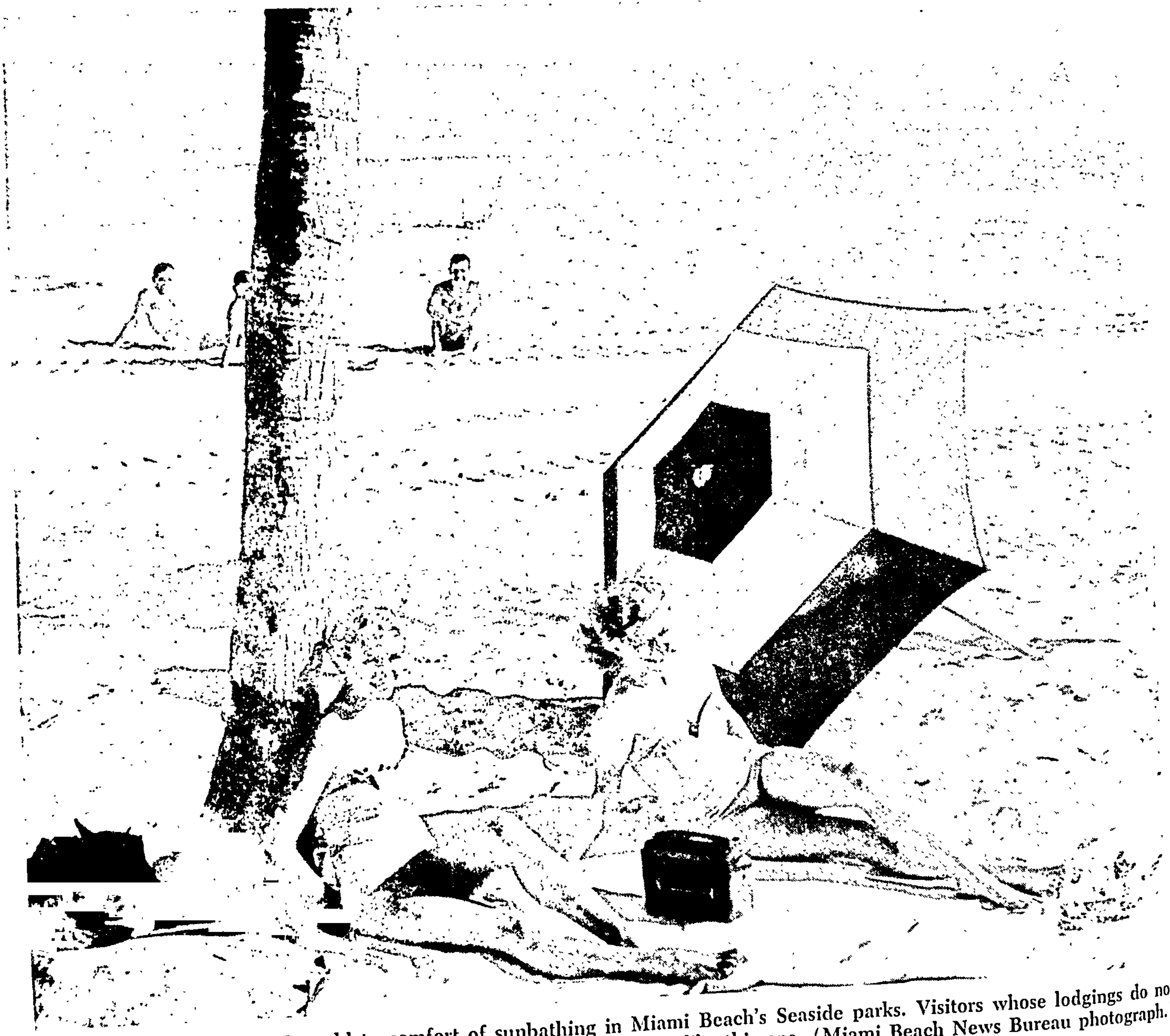
Georgetown University School of Medicine, Luncheon, Tuesday, June 14, 12:00 noon, Deauville Hotel, Baccarat Room. Tickets at $3.25 available from J. E. Fitzgerald, M.D., Georgetown University Medical Center, Georgetown Hospital, Washington 7, D. C., or the A. M. A. Alumni Registration Desk at Meeting.

Johns Hopkins University Alumni Association, Reception, Wednesday, June 15, 5:00 p. m., Carillon Hotel.

Marquette University Alumni Association, Luncheon, Tuesday, June 14, 12:30 p. m., Fontainebleau Hotel, Fleur De Lis Room. Tickets available from Marquette University Alumni Association, 620 N. 14th St., Milwaukee 3, Wis.

Mayo Alumni Association, Cocktail Party, Tuesday, June 14, 6:30 p. m., Roney-Plaza Hotel, Roney Gardens. Tickets at $2.50 available from F. Schmitt, M.D., 30 S. E. 8th St., Miami 32, Fla.

Alumnae Association, Woman's Medical College of Pennsylvania, Dinner, Wednesday, June 15, 6:30 p. m., The Carillon Hotel. Tickets at $7.50 available from Alumnae Office, 3300 Henry Ave., Philadelphia 29.



Radio and convenient palm add to comfort of sunbathing in Miami Beach's Seaside parks. Visitors whose lodgings do not provide private beaches or pools are always close to a public beach like this one. (Miami Beach News Bureau photograph.)

Hahnemann Medical College Alumni Association, Luncheon, Tuesday, June 14, 12:00 noon, Algiers Hotel. Tickets at $5 available from the A. M. A. Alumni Registration Desk at Meeting.

Harvard Medical Alumni Association, Cocktail Party, Wednesday, June 15, 5:30 p. m., Hotel Fontainebleau, Louis Philippe and Francine Rooms. Admission badges available from the A. M. A. Alumni Registration Desk at Meeting.

Henry Ford Hospital Medical Association, Cocktail Party, Tuesday, June 14, 5:30 p. m., Kenilworth Hotel, Card Room.

Alumni Association College of Medical Evangelists, Dinner, Wednesday, June 15, 6:30 p. m. Tickets available from the A. M. A. Alumni Registration Desk at Meeting. Place and price of tickets to be announced.

Alumni Association of the University of Chicago School of Medicine, Luncheon, Tuesday, June 14, 12:00 noon, Eden Roc Hotel. Tickets at $5 available from the Medical Alumni Association, University of Chicago, 950 E. 59th St., Chicago 37, and Ralph E. Kirsch, M.D., 1345 N. Bayshore Dr., Miami 32, Fla.

Obstetrics and Gynecology: Miami Beach Exhibition Hall, 1700 Washington Avenue, Room A. Convenes at 2 p. m., Tuesday, June 14.

Ophthalmology: Eden Roc Hotel, 45th and Collins Avenue, Mona Lisa Room. Convenes at 1:30 p. m., Tuesday, June 14.

Orthopedic Surgery: Fontainebleau Hotel, 4441 Collins Avenue, Fontaine Room. Convenes at 1 p. m., Tuesday, June 14.

Pathology and Physiology: Eden Roc Hotel, 45th and Collins Avenue, Pompeii Room. Convenes at 2 p. m., Tuesday, June 14.

Pediatrics: Fontainebleau Hotel, 4441 Collins Avenue, Fontaine Room. Convenes at 9 a. m., Wednesday, June 15.

Physical Medicine: Fontainebleau Hotel, 4441 Collins Avenue, French Room. Convenes at 9 a. m., Wednesday, June 15.

Preventive Medicine: Eden Roc Hotel, 45th and Collins Avenue, Pavilion Room. Convenes at 2 p. m., Tuesday, June 14.

Radiology: Fontainebleau Hotel, 4441 Collins Avenue, Pasteur Room. Convenes at 9 a. m., Wednesday, June 15.

Surgery, General: Miami Beach Exhibition Hall, 1700 Washington Avenue, Room A. Convenes at 9 a. m., Wednesday, June 15.

Urology: Fontainebleau Hotel, 4441 Collins Avenue, Pasteur Room. Convenes at 2 p. m., Tuesday, June 14.

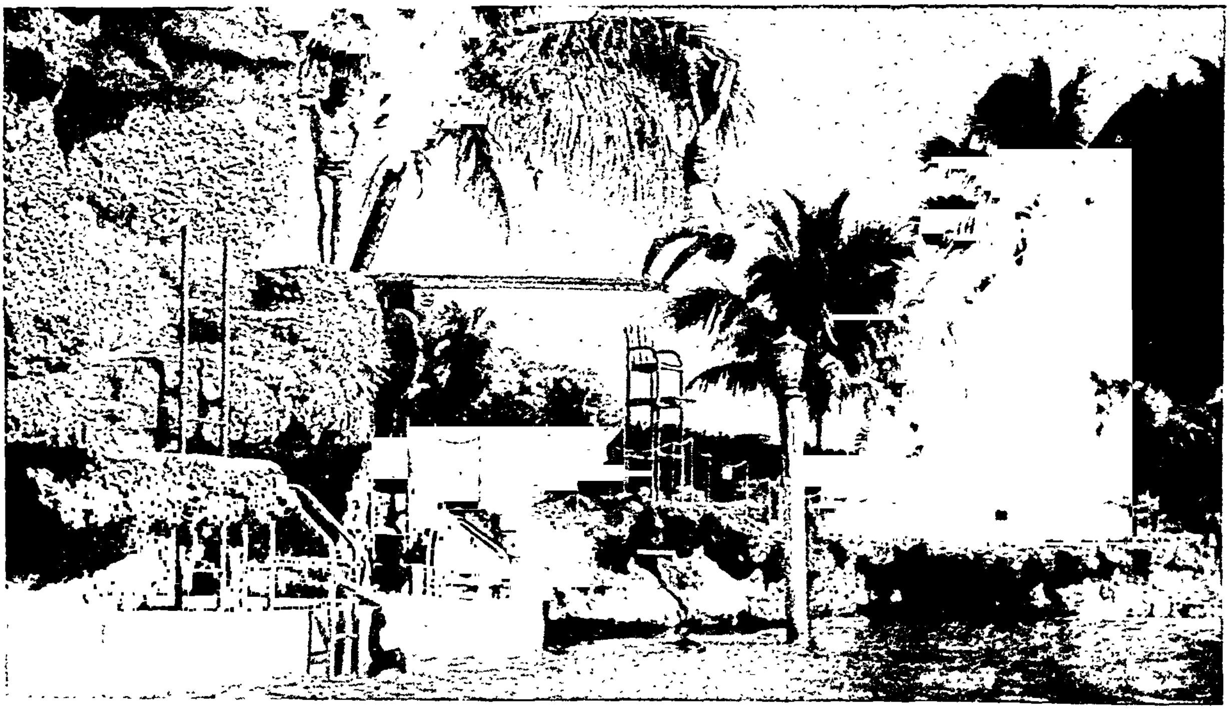
Miscellaneous Topics: Session on Aging: Fontainebleau Hotel, 4441 Collins Avenue, French Room. Convenes at 2 p. m., Wednesday, June 15.

Session on Allergy: Fontainebleau Hotel, 4441 Collins Avenue, Rosewood Room. Convenes at 2 p. m., Tuesday, June 14.

Meetings of Associated Groups

Association for Research in Ophthalmology, Inc.: Eden Roc Hotel, 45th and Collins Avenue, Mona Lisa Room. Convenes at 8:45 a. m., Monday, June 13.

Society for Investigative Dermatology, Inc., diLido Hotel, Lincoln and Collins Avenue, Cotillion Room. Convenes at 9 a. m., Monday, June 13.



Venetian Pool, over huge rockpit, in water playground with grotto, bridge, and beach, creates the illusion of hidden lagoon along picturesque Coral Gables Self-Guided Tour. (Miami-Metro News Bureau photograph.)

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Jesse Halpern
William Wickman
Marvin Meitus
Nicholas Tierney
Daniel Stone
D. Ward White

MEETING PLACES

House of Delegates: Americana Hotel, 9701 Collins Ave., Bal Harbour, Ballroom. House convenes at 10 a. m., Monday, June 13.

General Scientific Meetings: Fontainebleau Hotel, 4441 Collins Ave., Miami Beach, Ballroom. Sessions at 1:30 p. m., Monday, June 13, and at 9 a. m., Tuesday, June 14.

Scientific Exhibit: Miami Beach Exhibition Hall and Auditorium, 1700 Washington St., Miami Beach. Exhibit opens at 8:30 a.m., Monday, June 13, and closes at 12 noon, Friday, June 17.

Industrial Exhibit: Miami Beach Exhibition Hall and Auditorium, 1700 Washington St., Miami Beach. Exhibit opens at 8:30 a. m., Monday, June 13, and closes at 12 noon, Friday, June 17.

Dermatology: diLido Hotel, Lincoln and Collins Avenue, Cotillion Room. Convenes at 2 p. m., Tuesday, June 14.

Diseases of the Chest: Fontainebleau Hotel, 4441 Collins Avenue, La Ronde Room. Convenes at 1:45 p. m., Tuesday, June 14.

Experimental Medicine and Therapeutics: Fontainebleau Hotel, 4441 Collins Avenue, East Ballroom. Convenes at 2 p. m., Tuesday, June 14.

Gastroenterology and Proctology: Fontainebleau Hotel, 4441 Collins Avenue, West Ballroom. Convenes at 2 p. m., Tuesday, June 14.

General Practice: Fontainebleau Hotel, 4441 Collins Avenue, La Ronde Room. Convenes at 2 p. m., Tuesday, June 14.

The time to use a camera loaded with color film is when you visit Florida. This is Parrot Jungle near Miami where colorful travel snapshots can be taken, with a background of flamingos with rosy-white plumage and scarlet wing coverts.

Inaugural Meeting: Fontainebleau Hotel, 4441 Collins Ave., Miami Beach, Ballroom. Meeting begins at 8:30 p. m., Tuesday, June 14.

Motion Pictures: Miami Beach Exhibition Hall, Room B. Begins Monday afternoon, June 13, and continues through Friday morning, June 17.

Color Television: Miami Beach Auditorium, Room D. Begins Monday afternoon, June 13, and continues through Thursday, June 16.

Sections of Scientific Assembly

Anesthesiology: Fontainebleau Hotel, 4441 Collins Avenue, French Room. Convenes at 2 p. m., Tuesday, June 14.

Internal Medicine: Fontainebleau Hotel, 4441 Collins Avenue, East Ballroom. Convenes at 2 p. m., Tuesday, June 14.

Laryngology, Otology and Rhinology: Fontainebleau Hotel, 4441 Collins Avenue, Pasteur Room. Convenes at 9 a. m., Wednesday, June 15.

Military Medicine: Fontainebleau Hotel, 4441 Collins Avenue, La Ronde Room. Convenes at 2 p. m., Tuesday, June 14.

Nervous and Mental Diseases: Fontainebleau Hotel, 4441 Collins Avenue, West Ballroom. Convenes at 9 a. m., Wednesday, June 15.

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Jesse Halpern
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Louis M. Orr	Orlando, Fla.	
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M. L. Phelps	Denver
G. E. Twente	Jackson, Miss.
M. A. Vickers	Bangor, Maine
R. L. White	Boise, Idaho
Mr. C. Joseph Stetler, Secretary	Chicago

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Ralph W. Jack, Chairman

Frederick J. Waas
William M. Rowlett
Homer L. Pearson
Herbert L. Bryans
Orion O. Feaster
Edward Jelks
Leigh F. Robinson
Walter C. Jones
Eugene G. Peek Sr.
Shaler Richardson
William C. Thomas Sr.
Joseph S. Stewart
Walter C. Payne Sr.
Herbert E. White
David R. Murphey Jr.
Robert B. McIver
Frederick K. Herpel
Duncan T. McEwan
John D. Milton
Francis H. Langley
William C. Roberts
Jere W. Annis

Seminole Indians, who live and dress much as did their forefathers hundreds of years ago. (City of Miami News Burea photograph.)

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Joseph Jana Jr.
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Thomas Skaggs
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Julian Rickles
Maxwell Sayet
Karl Vetter

Registration Committee

Nelson Zivitz, Chairman

Seymour Alterman
Raymond Breitbart

BOARD OF DIRECTORS MEETING AND LUNCHEON

10:30 a. m. Meeting—Normandy Room
Mrs. Frank Gastineau, President, presiding
1:00 p. m. Luncheon
Richelieu Room

Press Room and National Headquarters Office—
Napoleon Room, Section I

CONVENTION PROGRAM

Monday, June 13

8:00 a. m. to 3:45 p. m. Registration and Exhibits
Napoleon Room, Section I
Hospitality Room
Charlemagne Room

ADDRESS OF WELCOME

Mrs. Wendell J. Newcomb, Immediate Past-President, Woman's Auxiliary to the Florida Medical Association

RESPONSE

Mrs. Joseph Black, President, Woman's Auxiliary to the Indiana State Medical Association

ROLL CALL

Mrs. W. W. Hubbard, Constitutional Secretary

PRESENTATION OF CONVENTION AGENDA

Mrs. Frank Gastineau

CONVENTION RULES OF ORDER

Mrs. Mason G. Lawson, Parliamentarian

NOMINATIONS FOR 1961 NOMINATING COMMITTEE AND PRESENTATION OF ELECTION COMMITTEE

CONVENTION ANNOUNCEMENTS

Mrs. Richard F. Stover, General Chairman

Largest flock of tame flamingos in the world live in the infield at Hialeah Race Course, open throughout the year to sightseers. (City of Miami News Bureau photograph.)

9:30 a. m. to 12:30 p. m. Formal opening of the thirty-seventh Annual Convention of the Woman's Auxiliary to the American Medical Association, Napoleon Room, Section III (lobby)
Mrs. Frank Gastineau, President, presiding

INVOCATION

Reverend Ronald S. Wilson, D.D., Minister, Westminster Presbyterian Church

PLEDGE OF LOYALTY TO THE WOMAN'S AUXILIARY

Mrs. E. Arthur Underwood, National Past-President

GREETINGS

Dr. Homer L. Pearson, Chairman, Committee on Arrangements, American Medical Association

Dr. Franklin J. Evans, President, Dade County Medical Association

REPORT OF CREDENTIALS AND REGISTRATION

Mrs. Wesley J. Nock, Chairman

MINUTES OF THE THIRTY-SIXTH ANNUAL CONVENTION

Mrs. W. W. Hubbard, Constitutional Secretary

ANNOUNCEMENT OF NATIONAL CONVENTION COMMITTEE APPOINTMENTS

REPORTS OF OFFICERS

President, Mrs. Frank Gastineau
President-Elect, Mrs. William Mackersie
First Vice President, Mrs. Charles L. Goodhand

PRESENTATION OF AUDITOR'S REPORT

Mrs. Harlan English, Treasurer

REPORT OF BOARD OF DIRECTORS

Mrs. Frank Gastineau

REPORT OF HISTORIAN

Mrs. George Turner

WOMAN'S AUXILIARY

A cordial invitation is extended to all members of the Woman's Auxiliary to the American Medical Association, their guests and the guests of physicians attending the convention of the American Medical Association, to participate in all social functions and attend the general meetings of the Auxiliary.

Headquarters will be at Hotel Deauville. Tickets for the various functions will be available at the registration desk (some also at convention hall). The Hospitality Room will be in the Charlemagne Room (lobby floor) and will be open from Sunday noon, June 12, to Thursday noon, June 16. Members and guests are cordially invited to visit the Room.

Please register early and secure your badge and program.

Teen-age Activities: A very interesting and entertaining program has been arranged for the elementary and teen-age children attending the convention, and all are cordially invited to participate. Cabana and pool party, sightseeing cruises, boat rides and ice skating are among the events planned. Details and tickets at the registration desk.

Mrs. Frank Gastineau, *President*
Mrs. Richard F. Stover, *Chairman*
Committee on Arrangements

Registration Hours

Sunday, June 12	12:30 p. m. to 4:00 p. m.
Monday, June 13	8:00 a. m. to 3:45 p. m.
Tuesday, June 14	9:00 a. m. to 4:00 p. m.
Wednesday, June 15	9:00 a. m. to noon

PRECONVENTION SCHEDULE

Saturday, June 11

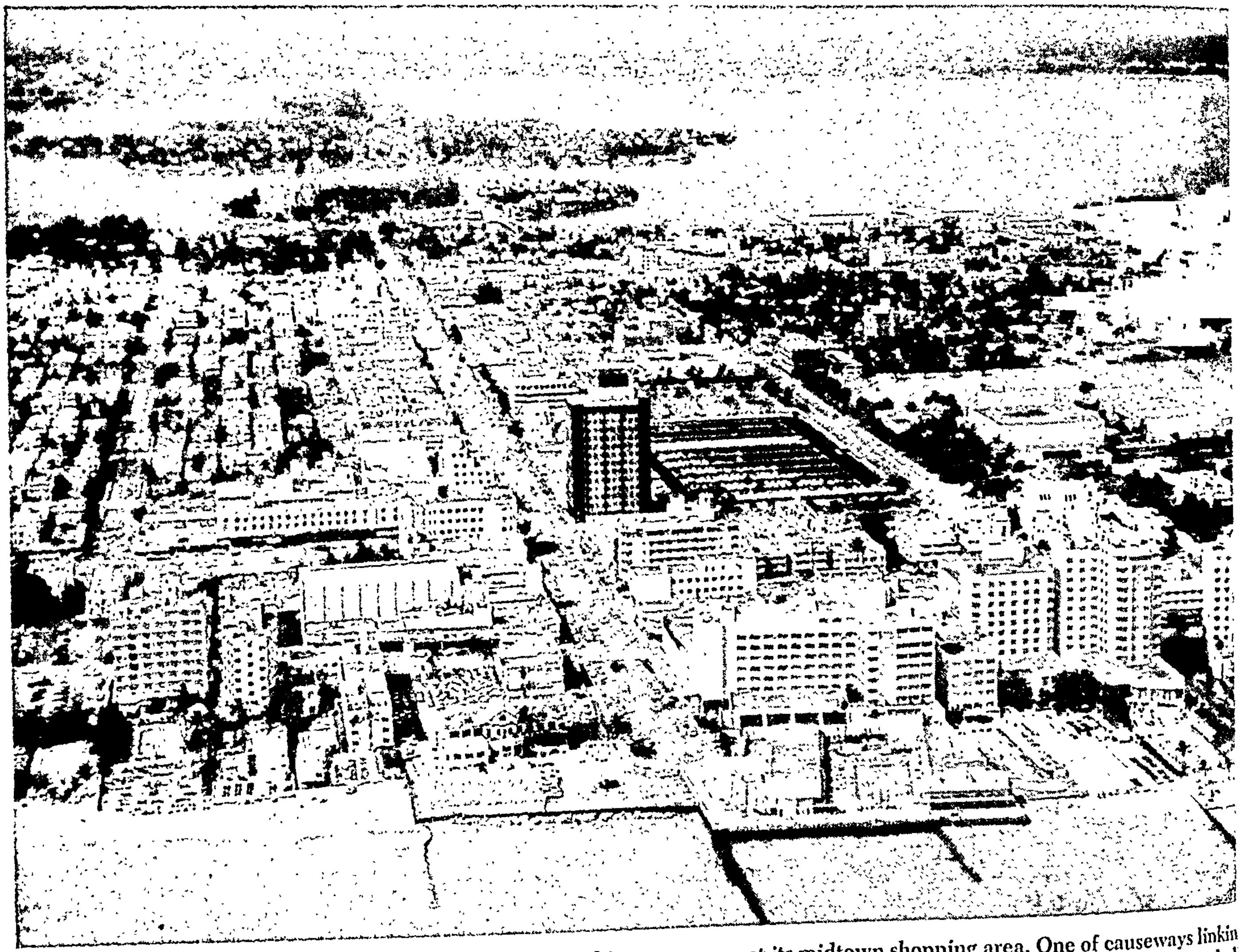
3:00 p. m.	Finance Committee Meeting Normandy Room (mezzanine floor) Mrs. Harry F. Pohlmann, Chairman

Sunday, June 12

12:30 p. m. to 4:00 p. m.	Registration and Exhibits Napoleon Room, Section I (lobby floor Hospitality Charlemagne Room (lobby floor)

COMMITTEE MEETINGS

2:30 p. m.	Resolutions Committee Normandy Room Mrs. Shelley C. Davis, Chairman
4:00 p. m.	Bylaws Committee President's Suite Mrs. C. Rodney Stoltz, Chairman



Looking westward from the sea, Miami Beach presents this appearance at its midtown shopping area. One of causeways linkin city with mainland island-hops across Biscayne Bay is in background. At far right is municipal Auditorium and convention hal (Miami Beach News Bureau photograph.)

STATE REPORTS—SOUTHERN REGION
Mrs. William G. Thuss, Moderator
Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, Oklahoma, South Carolina, Texas.

INTERMISSION

REPORT OF FINANCE COMMITTEE AND PRESENTATION OF 1960-61 BUDGET
Mrs. Harry F. Pohlmann, Finance Secretary

AMERICAN MEDICAL EDUCATION FOUNDATION
Mrs. Karl F. Ritter, Chairman

CIVIL DEFENSE SKIT
"Operation Home Preparedness"
Mrs. Neil W. Woodward, Chairman

STATE REPORTS—NORTHCENTRAL REGION
Mrs. Stephen C. Bachellor, Moderator
Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, Wisconsin.

REPORT OF LIAISON TO A. M. A. COUNCIL ON RURAL HEALTH
Mrs. Mason G. Lawson

REPORT OF LIAISON TO STUDENT, A. M. A. AUXILIARY
Mrs. William Mackersie

12:30 p. m.
Luncheon in honor of the Past Presidents of the Woman's Auxiliary to the American Medical Association—Richelieu Room.
Mrs. Frank Gastineau, President, presiding.
Grace: Mrs. Ralph B. Eusden, National Past-president.
Greetings: Dr. E. Vincent Askey, President-elect, American Medical Association.
Guest Speaker: Dr. Louis M. Orr, President, American Medical Association.
Presentation of Woman's Auxiliary Contribution to the American Medical Education Foundation.
Mrs. Frank Gastineau.
Presentation of A. M. E. F. Awards.
Dr. George F. Lull, President, American Medical Education Foundation.
Presentation of Ethel Gastineau Trophy.
Dr. George F. Lull.
Presentation of County Achievement Awards.
Mrs. Karl F. Ritter, A. M. E. F. Chairman.
Guests of Honor: Dr. Louis M. Orr, President, American Medical Association; Dr. E. Vincent Askey, President Elect; Dr. Leonard W. Larson, Chairman Board of Trustees; Dr. F. J. L. Blasingame, Executive Vice President; Dr. Ernest B. Howard, Assistant Executive Vice President; and the wives of Officers and Trustees, American Medical Association.
Tickets (including tax and gratuity), $4.00.

TUESDAY, JUNE 14
Afternoon Meeting

2:30 p. m.

MENTAL HEALTH PRESENTATION
Mrs. Aaron Margulis, Chairman,
"A Doctor's Mental Health Begins at Home."

STATE REPORTS—WESTERN REGION
Mrs. L. D. Jacobson, Moderator,
Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington, Wyoming.

PARAMEDICAL CAREERS RECRUITMENT PRESENTATION
Mrs. Lawrence Rapee, Chairman.

4:30 p. m. to 5:00 p. m. SAFETY COMMITTEE PRESENTATION
Hotel Deauville Swimming Pool
Mrs. Samuel S. Lombardo, Chairman
Water Safety Demonstration by Dade County Chapter, American Red Cross.

8:00 p. m. OPENING MEETING OF THE AMERICAN MEDICAL ASSOCIATION
Fontainebleau Hotel.

10:00 p. m. RECEPTION AND BALL IN HONOR OF THE PRESIDENT OF THE AMERICAN MEDICAL ASSOCIATION
Fontainbleau Hotel.

WEDNESDAY, JUNE 15

8:00 a. m. to 5:00 p. m. HOSPITALITY
Charlemagne Room.

9:00 a. m. to 12:00 noon REGISTRATION AND EXHIBITS
Napoleon Room, Section I.

GENERAL MEETING
Napoleon Room III.
Mrs. Frank Gastineau, presiding.

MINUTES
Mrs. W. W. Hubbard.

CONVENTION ANNOUNCEMENTS
Mrs. Richard F. Stover.

REPORT OF CREDENTIALS AND REGISTRATION
Mrs. Wesley J. Nock.

NEW BUSINESS
Amendments to Bylaws,
Mrs. C. Rodney Stoltz, Chairman.
Resolutions,
Mrs. Shelley C. Davis, Chairman.
Courtesy Resolutions,
Mrs. William A. Garrott, Chairman.

ELECTION OF OFFICERS

INSTALLATION OF OFFICERS
Mrs. Mason G. Lawson, National Past-President.

PRESENTATION OF PAST PRESIDENT'S PIN
Mrs. E. Arthur Underwood, National Past-President.

PRESENTATION OF PRESIDENT'S PIN AND GAVEL
Mrs. Frank Gastineau, Immediate Past-President.

INAUGURAL ADDRESS
Mrs. William Mackersie.

ADJOURNMENT

* * *

12:00 p. m. to 1:30 p. m. Informal fixed-menu luncheon—Charlemangne Room. Tickets $2.75 including tax and gratuity. Reservations requested before 10:00 a. m.

* * *

1:30 p. m. Meeting of the Board of Directors. Baccarat Room (Mezzanine).
Mrs. William Mackersie, President, presiding.

2:30 p. m. Informal discussion 1960-1961 Committee Programs (Board of Directors and National Committee Chairmen).
Mrs. William Mackersie, presiding.

THURSDAY, JUNE 16

8:00 a. m. to 12:00 noon Hospitality.
Charlemagne Room.

9:30 a. m. to 12:00 noon Films (titles to be announced).
Napoleon Room, Section II.

12:00 noon to 1:30 p. m. Informal fixed-menu luncheon. Charlemagne Room. Tickets $2.75, including tax and gratuity. Reservations requested before 10:00 a. m.

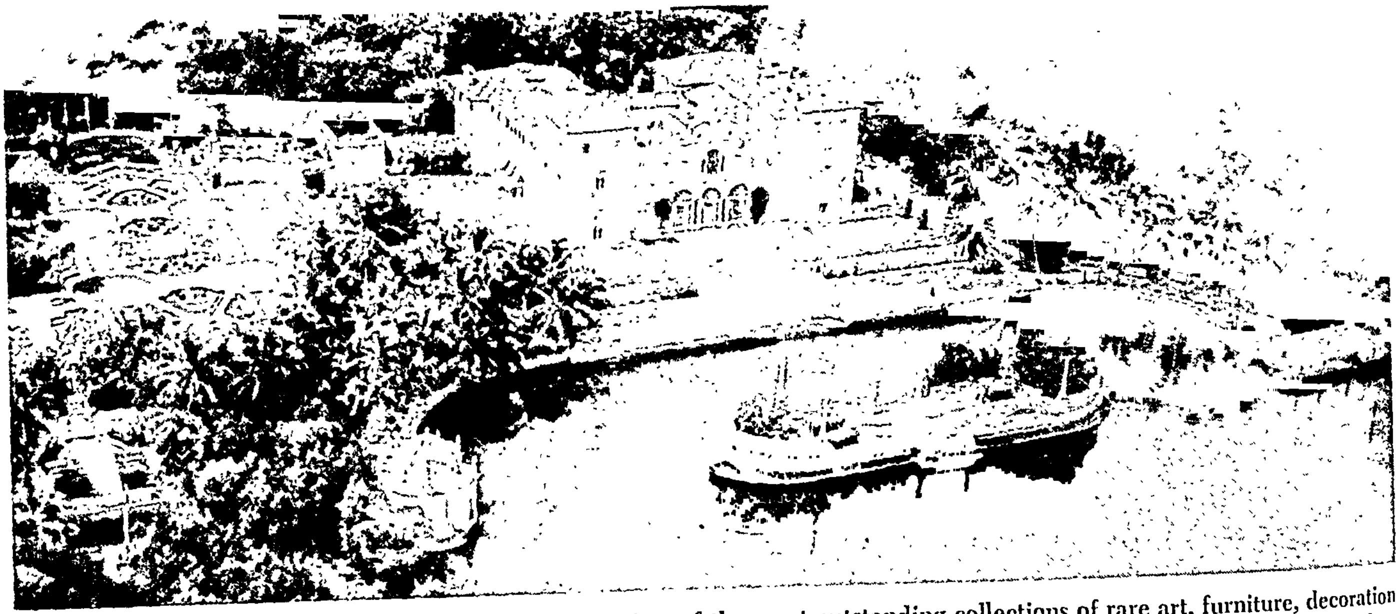
1:30 p. m. to 3:25 p. m. Round table discussions—Members invited. Round tables will be presented on three levels, based on membership in each state.

REPORT OF HEADQUARTERS OFFICE
Miss Margaret Wolfe, Executive Secretary
REPORT OF 1960 NOMINATING COMMITTEE (first reading)
Mrs. E. Arthur Underwood, Chairman
MEMORIAL SERVICE
Mrs. Eugene Countiss, President, Woman's Auxiliary to the Louisiana State Medical Society

1:00 p. m. to 3:30 p. m. VOTING FOR 1961 NOMINATING COMMITTEE
Polling Place: Normandy Room (mezzanine floor)
Mrs. C. A. Colombi, Chairman, Election Committee

4:00 p. m. to 6:00 p. m. TEA AND FASHION SHOW—CASANOVA ROOM (lobby floor)
Honoring Mrs. Frank Gastineau, President, and Mrs. William Mackersie, President-elect
Bulletin Birthday Celebration—21st Anniversary
Mrs. F. Erwin Tracy, Chairman, Circulation Committee
Mrs. E. M. Egan, Chairman, Publications Committee
Mrs. James P. Simonds, Honorary Emeritus Chairman
Mrs. Rollo K. Packard, National President, 1939-40
Special Guests: Members of the National Board of Directors, National Committee Chairman, State Presidents and Presidents Elect, and wives of officers and trustees of the American Medical Association
Hostesses: Woman's Auxiliary to the Florida Medical Association, Inc., and to the Dade County Medical Society, Inc.
Compliments of Pfizer Laboratories and J. B. Roerig and Company, Divisions of Chas. Pfizer and Co., Inc.
Admission by ticket only, which can be secured at the time of registration. Number limited.

12:00 noon to 2:00 p. m. Informal fixed-menu luncheon—Charlemagne Room (lobby floor). Tickets $2.75, including tax and gratuity.
Reservations requested before 10 a. m.



Fabulous $15,000,000 Deering estate and mansion. One of the most outstanding collections of rare art, furniture, decorations, and formal gardens. Great 17th Century Italian 20-room house rises on Biscayne Bay across from amazing sculptured stone boat. (Florida State News Bureau photograph.)

Data posters on A. M. E. F., Bulletin Circulation and Membership will be on display during the entire convention and will take the place of statistical reports on these projects.

TUESDAY, JUNE 14

8:00 a. m. to 4:00 p. m. REGISTRATION AND EXHIBITS
Napoleon Room, Section I
HOSPITALITY
Charlemagne Room

9:00 a. m. to 5:00 p. m. GENERAL MEETING of the Woman's Auxiliary to the American Medical Association
Napoleon Room, Section III
Mrs. Frank Gastineau, presiding
MINUTES
Mrs. W. W. Hubbard
CONVENTION ANNOUNCEMENTS
Mrs. Richard F. Stover
TELLERS REPORT: Election of 1961 Nominating Committee
Mrs. C. A. Colombi, Chairman
STATE REPORTS—EASTERN REGION
Mrs. Paul E. Rauschenbach, Moderator
Connecticut, Delaware, District of Columbia, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, West Virginia
"WORDS AT WORK IN THE AUXILIARY"
John Bach, Division of Communications, American Medical Association
Mr. Bach will recount the importance of words in all kinds of medical communication, both from the standpoint of the doctor and his wife in the Auxiliary. The work which members of the Auxiliary can do with words in behalf of medicine is important to the medical profession, but what they say and how they say it carries a grave responsibility.
TODAY'S HEALTH PROJECT
Robert Enlow, Dir.,
Circulation and Records, A. M. A.
LEGISLATION PRESENTATION
Mrs. Leo Smith, Chairman
A. M. A. platform for political action

HOSPITALITY

Mrs. R. Spencer Howell—Chairman
Mrs. Robert Dickey—Co-chairman
Mrs. William P. Smith—Co-chairman
Mrs. John Butcher
Mrs. A. E. Drexel
Mrs. Edward Ludwig
Mrs. Wendall Newcomb
Mrs. Lee Rogers Jr.
Mrs. Dean Steward
Mrs. Abbott Wilcox
Mrs. S. J. Wilson
and members of The Woman's Auxiliary
to the Florida State Medical Association

INFORMATION

Mrs. M. M. Greenfield—Chairman
Mrs. Robert Mikell—Co-chairman
Mrs. Richard Clay
Mrs. Manuel Gonzalez
Mrs. H. W. Gray
Mrs. Carlton Howard
Mrs. Carlos Lamar
Mrs. Lawrence Medoff
Mrs. James Robertson
Mrs. Donald Smith
and members of The Woman's Auxiliary
to the Dade County Medical Association, Inc.

LUNCHEON

Mrs. William P. Smith—Chairman
Mrs. Arthur Wood Jr.—Co-chairman
Mrs. James Anderson
Mrs. O. W. Burtner
Mrs. R. B. Chrisman
Mrs. Burns Dobbins
Mrs. L. W. Dowlen
Mrs. Charles Ettinger
Mrs. B. David Epstein
Mrs. Richard Fleming
Mrs. Thomas Guyton
Mrs. Francis Holland
Mrs. David Howell
Mrs. Robert Isham
Mrs. Ulfar Jonsson
Mrs. Robert Lawson
Mrs. Meredith Mallory
Mrs. Donald Marion
Mrs. Frederick Meadows
Mrs. William Mixson
Mrs. Harold Spear
Mrs. Robert Tindall
Mrs. Frank Woods
Mrs. Frederick Zaugg

MEETING ROOMS

Mrs. William L. Fitzgerald—Chairman
Mrs. E. W. Cullipher—Co-chairman

MUSIC

Mrs. James Anderson—Chairman
Mrs. Donald Altman—Co-chairman

PAGES

Mrs. Francis N. Cooke—Chairman
Mrs. Donald Marion—Co-chairman
Mrs. Henry Bryant
Mrs. M. C. Martin
Mrs. R. K. Nuzum
and members of The Woman's Auxiliary
to the Dade County Medical Association, Inc.

PUBLICITY

Mrs. John Dix—Chairman
Mrs. George Turke Jr.—Co-chairman
Mrs. Martin Rosenthal

REGISTRATION

Mrs. Wesley S. Nock—Chairman
Mrs. Henry Caffee—Co-chairman
Mrs. Andrew Brown
Mrs. John Hicks
Mrs. Leonard Jacobson
Mrs. William Shaver
Mrs. Donald Smith
Mrs. D. Ward White
and members of The Woman's Auxiliary
to the Dade County Medical Association, Inc.

TEA

Mrs. Franklin J. Evans—Chairman
Mrs. Wayne Martin—Co-chairman
Mrs. James Anderson
Mrs. Edward Annis
Mrs. Maurice Cooper
Mrs. Ernest Ellis
Mrs. Eugene Flipse
Mrs. Kermit Gates
Mrs. Frank Hewlitt
Mrs. Carlton Howard
Mrs. Emil Isberg
Mrs. Albert Jaslow
Mrs. Cal Kellogg
Mrs. James Robertson
Mrs. Walter Sackett
Mrs. Ralph Sappenfield
Mrs. Howard Simon Jr.
Mrs. George Schmitt
Mrs. Chauncey Stone
Mrs. George Turke Jr.
Mrs. Arthur Wood Jr.
Mrs. Thomas Zaydon

YOUTH ACTIVITIES

Mrs. Leon Mannheimer—Chairman
Mrs. Sherman Kaplan—Co-chairman
and members of The Woman's Auxiliary
to the Dade County Medical Association, Inc.
Children of Auxiliary Members

TICKETS

Mrs. William Wickman—Chairman
Mrs. Harrien Gray—Co-chairman
and members of The Woman's Auxiliary
to the Dade County Medical Association, Inc.

Attendees are asked to go to room of their auxiliary membership category. Subject matter will be prepared with the size and scope of membership in mind.

Napoleon Room II—Auxiliaries with membership under 1,000: Alaska, Arizona, Arkansas, Delaware, District of Columbia, Hawaii, Idaho, Maine, Maryland, Mississippi, Montana, Nebraska, Nevada, New Hampshire, New Mexico, North Dakota, Oregon, Rhode Island, South Carolina, South Dakota, Utah, Vermont, Wyoming.

Chairman: Mrs. Hiram D. Cochran, Arizona.

Timekeeper: Mrs. Mark A. Yessian, Rhode Island.

1:30 p.m. Community Service
to Mrs. John Wagner, Moderator.
2:05 p.m.

2:10 p.m. Membership
to Mrs. Charles L. Goodhand, Moderator.
2:45 p.m.

2:50 p.m. Program
to Mrs. Rudolph T. Unruh, Moderator.
3:25 p.m.

Napoleon Room I—Auxiliaries with membership 1,000 to 2,000: Alabama, Colorado, Connecticut, Georgia, Iowa, Kansas, Kentucky, Louisiana, Missouri, Oklahoma, Tennessee, Virginia, Washington, West Virginia, Wisconsin.

Chairman: Mrs. Albert E. Goldstein, National Director.

Timekeeper: Mrs. Ralph K. Bush, New Jersey.

1:30 p.m. Membership
to Mrs. Charles L. Goodhand, Moderator.
2:05 p.m.

2:10 p.m. Program
to Mrs. Rudolph T. Unruh, Moderator.
2:45 p.m.

2:50 p.m. Community Service
to Mrs. John Wagner, Moderator.
3:25 p.m.

Napoleon Room III—Auxiliaries with membership over 2,000: California, Florida, Illinois, Indiana, Massachusetts, Michigan, Minnesota, New Jersey, New York, North Carolina, Ohio, Pennsylvania, Texas.

Chairman: Mrs. Stanley Truman, National Director.

Timekeeper: Mrs. Milton W. Kogan, New York.

1:30 p.m. Program
to Mrs. Rudolph T. Unruh, Moderator.
2:05 p.m.

2:10 p.m. Community Service
to Mrs. John Wagner, Moderator.
2:45 p.m.

2:50 p.m. Membership
to Mrs. Charles L. Goodhand, Moderator.
3:25 p.m.

Napoleon Room II—Postconvention Planning Meeting

For National officers, directors, committee chairmen, state presidents and presidents elect.

Mrs. William Mackersie, President, presiding.

3:35 p.m. Coffee

4:00 p.m. Discussion of 1960-1961 Programs by National Chairmen

5:00 p.m. News from the A. M. A. House of Delegates
Ernest B. Howard, M.D.,
Asst. Executive Vice President, A. M. A.

NATIONAL CONVENTION COMMITTEES

Nominating: Mrs. E. Arthur Underwood, Chairman, Mrs. Paul E. Rauschenbach, Mrs. F. Erwin Tracy, Mrs. Leo J. Schaefer, Mrs. Haskell D. Hatfield, Mrs. E. R. W. Fox, Mrs. S. P. Esposito.

Reading Convention Minutes: Mrs. E. M. Egan, Chairman, Mrs. W. W. Hubbard, Mrs. Mason G. Lawson, Miss Margaret Wolfe.

Resolutions: Mrs. Shelley C. Davis, Chairman, Mrs. John T. Morris, Mrs. C. C. Long, Mrs. John Van Prohaska, Mrs. Lemuel C. McGee.

Resolutions—Courtesy: Mrs. William A. Garrott, Chairman, Mrs. S. H. Ambrose, Mrs. Clifford Harwood, Mrs. Jordan Kelling, Mrs. James T. Thompson.

Election (and Tellers): Mrs. C. A. Colombi, Chairman, Mrs. Walter E. Penta, Mrs. Robert R. Pittman, Mrs. Harold Gay, Mrs. Morton Arnold, Mrs. Robert L. Garrard, Mrs. George O. Rowohlt.

Timekeepers: Mrs. Harry W. Buzzard, Chairman, Mrs. John J. Ramsbottom, Mrs. Samuel Gendel, Mrs. Kenneth E. Prescott, Mrs. Walter A. Porter, Mrs. Milton W. Kogan, Mrs. Preston Brogdon.

LOCAL ARRANGEMENTS COMMITTEES

General Chairman, Mrs. Richard F. Stover

HONORARY CHAIRMEN

Mrs. Wendall J. Newcomb
Mrs. John Butcher
Mrs. R. Spencer Howell
Mrs. Wesley S. Nock

SECRETARY TO THE COMMITTEES

Mrs. Robert P. Keiser

DECORATIONS

Mrs. Nicholas Tierney—Chairman
Mrs. O. W. Burtner—Co-chairman
Mrs. James Anderson
Mrs. A. E. Drexel
Mrs. Richard Fleming
Mrs. Frank Hewlitt
Mrs. Harold Unger

FAVORS

Mrs. James Ferguson—Chairman
Mrs. Herman Boughton—Co-chairman
Mrs. John Butcher
Mrs. Richard Dever
Mrs. Erwin Hoffman
Mrs. Edward Ludwig
Mrs. Wendall Newcomb
Mrs. Lee Rogers Jr.
Mrs. Dean Steward
Mrs. Harold Unger
Mrs. Abbott Wilcox
Mrs. S. J. Wilson
and members of The Woman's Auxiliary
to the Florida State Medical Association

FINANCE

Mrs. Perry D. Melvin—Chairman
Mrs. Frank Gastineau
Mrs. Richard Stover
Miss Margaret Wolfe

Representative to Scientific Exhibit—Edwin L. Rushia, Augusta, Ga.

Executive Committee—John Adriani, New Orleans; Meyer Saklad; Alice McNeal; Vincent J. Collins, and Joseph H. Failing.

Tuesday, June 14—2 p. m.

FONTAINEBLEAU HOTEL, FRENCH ROOM

BUSINESS MEETING; PRESENTATION OF RESOLUTIONS; REPORT OF DELEGATE; INTRODUCTION OF SCIENTIFIC EXHIBITORS

Symposium on Problems in Anesthetic Management

Dilutional Hypervolemia During Transurethral Resection of the Prostate.
Gertie F. Marx, James W. Koenig, and Louis R. Orkin, New York.

Depression of Cardiac Output by the Induction of Anesthesia.
Haviland Flickinger, William Fraimow, Richard T. Cathcart, and Thomas F. Nealon Jr., Philadelphia.

Body Temperature of Infants and Children During Anesthesia.
C. R. Stephen and Sara J. Dent, Durham, N. C.

The Anesthetic Hazards of Obesity.
Alfred J. Catenacci, Dale Boersma, and John D. Anderson, Philadelphia.

The Crushed Chest Injury and the Anesthesiologist.
William Hamelberg, James Dindot, and William Mentges, Columbus, Ohio.

Anesthetic Problems in Poliomyelitis Respirator Patients.
Milton H. Adelman, Philip A. Lief, and Avron Y. Sweet, New York.

The Preanesthetic Evaluation and Preparation of the Patient with Peripheral Edema.
Robert L. Chester and Kenneth K. Keown, Columbia, Mo.

Progressive Loss of Protective Reflexes in the Airway with the Advance of Age.
Henning Pontoppidan and Henry K. Beecher, Boston.

Wednesday, June 15—2 p. m.

MIAMI BEACH EXHIBITION HALL, ROOM A

JOINT MEETING WITH THE SECTIONS ON OBSTETRICS AND GYNECOLOGY, PATHOLOGY AND PHYSIOLOGY, AND GENERAL SURGERY

Symposium on Operating Room Fatalities

Moderator: Henry K. Beecher, Boston

Introduction. Henry K. Beecher, Boston.
Surgical Aspects. Curtis P. Artz, Jackson, Miss.
Obstetrical and Gynecological Aspects. James H. Ferguson, Miami, Fla.
Anesthesiologist's Viewpoint. Jay Jacoby, Milwaukee.
Pathologist's Viewpoint. Milton Helpern, New York.
Panel Discussion.

Thursday, June 16—2 p. m.

FONTAINEBLEAU HOTEL, FRENCH ROOM

BUSINESS MEETING; ELECTION OF OFFICERS

Chairman's Address. Meyer Saklad, Providence, R. I.

Trends in Medical Education of Significance to Anesthesiology. M. T. Jenkins, Dallas, Texas.

Is the Preoperative Use of Antiemetics Justified?
F. W. Summers, S. O. Antony, and John Adriani, New Orleans.

Potentiation of Meperidine by Promethazine.
Arthur S. Keats, Jane Telford, and Yoshio Kurosu, Houston, Texas.

Medical Hypnosis for Obstetrics; A Clinical and Biochemical Evaluation of the Newborn.
Frank Moya and L. Stanley James, New York.

Use of Toxiferine for the Production of Surgical Relaxation.
Francis F. Foldes, Bernard Wolfson, and Martin Sokoll, Pittsburgh.

Comparison of Experimental Analgesic Drugs: (Win 14,098-Brand of Piminodine, Win 14,265-2 and Win 14,465-2) with Meperidine in Man Using a Double-Blind Technique.
Albert M. Betcher, Chiu-Yum-San, Alfred N. Godholm, and Jetty Alter, New York.

Muscle Pain After Succinylcholine: A Comparative Study.
Melvin Pick, Colorado Springs, and W. Curtis Pearcy, Denver.

The Explosion Hazard of Intra-Gastric Anesthetic Mixtures.
Beatriz L. de Nava and Thomas F. McDermott, Washington, D. C.

SECTION ON DERMATOLOGY

OFFICERS OF SECTION

Chairman—Wiley M. Sams, Miami, Fla.
Vice-chairman—William J. Morginson, Salt Lake City.
Secretary—Edward P. Cawley, Charlottesville, Va.
Assistant Secretary—Harry L. Arnold Jr., Honolulu, Hawaii.
Delegate—Winfred A. Showman, Tulsa, Okla.
Representative to Scientific Exhibit—Stanley E. Huff, Evanston, Ill.
Executive Committee—Clarence S. Livingood, Detroit; Wiley M. Sams; William J. Morginson; Edward P. Cawley, and Winfred A. Showman.

Program of Section on Dermatology

Tuesday, June 14—2 p. m.

DI LIDO HOTEL, COTILLION ROOM

BUSINESS MEETING

Chairman's Address: Photosensitizing Therapeutic Agents.
Wiley M. Sams, Miami, Fla.

Experiments in Protection from Total Body Irradiation.
J. M. Knox, A. C. Griffin, R. E. Hakim, H. D. Bennett, H. L. Barton, V. P. Collins, and R. G. Freeman, Houston, Texas.

Ioquin in the Treatment of Seborrheic Dermatitis of Scalp and Skin.
Eugene S. Bereston and Daniel P. Roberts, Baltimore.

Isolation of Wart Virus in Tissue Culture and Subsequent Re-Inoculation into Human Volunteers.
Charles G. Mendelson, Fort Jackson, S. C., and Albert M. Kligman, Philadelphia.

Long-Term Systemic Use of Tetracycline in Acne.
Theodore Cornbleet, Chicago.

Quantitative Estimation of Skin Mobility in Scleroderma.
Daniel M. Bachman, Portland, Ore.

Liquid Nitrogen in the Treatment of Skin Diseases.
J. M. Greenhouse, Hollywood, Fla.

PROGRAM OF THE SCIENTIFIC ASSEMBLY

GENERAL SCIENTIFIC MEETINGS

Monday, June 13–1:30 p. m.

FONTAINEBLEAU HOTEL, GRAND BALLROOM

Presiding: Carl A. Lincke, Carrollton, Ohio
Chairman, Council on Scientific Assembly

1:30 p. m.

The Joseph Goldberger Lecture in Clinical Nutrition: The Role of the Vitamins in the Etiology and Treatment of Anemia.

Richard W. Vilter, Director, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati.

Monday, June 13–2 p. m.

Presiding: Alphonse McMahon, St. Louis
Member, Council on Scientific Assembly

Symposium on Nutrition

2:00 p. m

The Two-Carbon Chain at the Crossroads of Metabolism.

Robert E. Olson, Professor and Head, Department of Biochemistry and Nutrition, University of Pittsburgh Graduate School of Public Health, Pittsburgh.

2:30 p. m.

Highlights on the Cholesterol: Fats, Diets and the Atherosclerosis Problems.

Grace A. Goldsmith, Professor of Medicine, Tulane University School Medicine, New Orleans.

3:00 p. m.

The B Complex Vitamins: Their Functions and Use in Clinical Medicine.

Robert E. Shank, Danforth Professor of Preventive Medicine, Washington University School of Medicine, St. Louis.

3:30 p. m.

Nutritional Management of the Chronic Diarrheas–Adults.

Frank H. Gardner, Assistant Professor of Medicine, Harvard Medical School, Boston.

4:00 p. m.

Nutritional Management of the Chronic Diarrheas–Children.

Paul A. di Sant Agnese, Chief, Pediatric Metabolism Branch, National Institute of Arthritis and Metabolic Diseases, Department of Health, Education and Welfare, Bethesda, Md., and Clinical Professor of Pediatrics, Georgetown University School of Medicine, Washington, D. C.

4:30 p. m.

Nutrition to Aid in Recovery and Rehabilitation from Injuries.

Stanley M. Levenson, Chief, Department of Surgical Metabolism, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C.

Tuesday, June 14–9 a. m.

FONTAINEBLEAU HOTEL, GRAND BALLROOM

Presiding: Michael E. De Bakey, Houston, Texas
Member, Council on Scientific Assembly

Symposium on Evaluation and Preparation of the Patient for Anesthesia and Surgery

Presented in cooperation with the Sections on Anesthesiology, Diseases of the Chest, General Practice, Internal Medicine, Pathology and Physiology, Pediatrics, and General Surgery.

9:00 a. m.

Operative Risk and Physical Status.

Meyer Saklad, Director of Anesthesia, Rhode Island Hospital, Providence, R. I.

Role of Family Physician in Preparing a Patient for Surgical Exploration.

Thomas E Rardin, Past-president, Ohio Academy of General Practice, Columbus, Ohio.

The Psychological Preparation.

Eugene S. Turrell, Professor and Chairman, Department of Psychiatry, Marquette University School of Medicine–Milwaukee Sanitarium, Milwaukee.

Cardiac Evaluation and Preparation.

John S. La Due, Associate Professor of Clinical Medicine, Cornell University Medical School, New York.

Evaluation and Correction of Electrolyte Blood and Fluid Balance.

Arlie R. Mansberger Jr., Assistant Professor of Surgery, University of Maryland School of Medicine, Baltimore, Md.

Respiratory Evaluation and Risk.

George R. Meneely, Associate Professor of Medicine, Vanderbilt University School of Medicine, Nashville, Tenn.

Preparation of Children.

Robert M. Smith, Director, Department of Anesthesia, Children's Hospital, Boston.

Preparation of Geriatric Patients.

C. Rollins Hanlon, Professor of Surgery and Director, Department of Surgery, St. Louis University School of Medicine, St. Louis.

THE PROGRAMS OF THE SECTIONS

OUTLINE OF THE SCIENTIFIC PROCEEDINGS

The following papers are announced to be read before the various sections. The order here is not necessarily the order that will be followed in the Official Program. The Official Program will be similar to the programs issued in previous years and will contain the final program of each section with abstracts of the papers, as well as the scientific exhibits, the program of the Inaugural meeting, and other information. To prevent misunderstandings and protect the interest of advertisers, it is here announced that this Official Program will contain no advertisements. It is copyrighted by the American Medical Association and will not be distributed before the session. A copy will be given to each physician on registration.

SECTION ON ANESTHESIOLOGY

OFFICERS OF SECTION

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Vice-Chairman–Alice McNeal, Birmingham, Ala.
Secretary–Vincent J. Collins, New York.
Assistant Secretary–Kenneth K. Keown, Columbia, Mo.
Delegate–Joseph H. Failing, Los Angeles.

Studies on the Location of the Receptor Site in Cutaneous Axon Reflexes.
Robert Auerbach, Roger W. Pearson and Allan L. Lorincz, Chicago.

The Modulating Influence of Stroma on Cells Derived from the Epidermis Studied in Human Auto-Transplants.
E. J. Van Scott and R. P. Reinertson, Bethesda, Md.

Keratinization in Human Epidermal Auto-Implants.
Richard P. Reinertson, Bethesda, Md.

Transplantation of Melanocytic Nevi to Vitiliginous Skin.
Otto C. Stegmaier, Chicago.

A Contribution on the Mechanism of Vesiculation in Human Skin.
Gerd K. Steigleder and David R. Weakley, New York.

Electron Microscope Studies of Dermal-Epidermal Separation in Human Skin.
Roger W. Pearson and Benjamin Spargo, Chicago.

An Electronmicroscopic Study of Acantholysis in Pemphigus Vulgaris.
George F. Wilgram, James B. Caulfield, and Walter F. Lever, Boston.

Wednesday, June 15—9 a. m.

DI LIDO HOTEL, COTILLION ROOM

Measurement of Cutaneous Anti-Inflammatory Activity of ACTH and Corticosteroids in Man.
William L. Epstein and Vincent DiRaimondo, San Francisco.

Attempts to Transfer Eczematous Contact-Type Allergy with Whole Blood Transfusions.
Leonard C. Harber and Rudolf L. Baer, New York.

Effects of Thyroid Hormone on the Skin.
Ruth K. Freinkel, Boston.

Cheilitis of Mongolism.
Thomas Butterworth, Reading, Pa., Eugene P. Leoni, Norristown, Pa., Herman Beerman and Margaret Gray Wood, Philadelphia, and Lyon P. Strean, Norristown, Pa.

Some Bacteriological Data on Dermatological Patients.
James E. Greer, Richard R. Menard, and Clarence S. Livingood, Detroit.

Macroscopic Histochemistry of Fungi.
H. L. Roth and R. K. Winkelmann, Rochester, Minn.

Immunochemical Studies on Dermatophyte Fungi. II. The Antigenic Characteristics of Dermatophyte Cell Wall Polysaccharides.
Thomas H. Sternberg, Earl G. McNall, Lloyd J. Sorensen, and Victor D. Newcomer, Los Angeles.

Inhibition of Growth of Pathogenic Yeasts by Human Serum.
Frank J. Roth Jr., Martin I. Goldstein, and Harvey Blank, Miami, Fla.

Experimental Inoculation of Tinea Versicolor to Human Subjects. Ruth C. Burke, New Haven, Conn.

SECTION ON DISEASES OF THE CHEST

OFFICERS OF SECTION

Chairman—Seymour M. Farber, San Francisco.
Vice-chairman—Herman J. Moersch, Rochester, Minn.
Secretary—Burgess L. Gordon, Albuquerque, N. Mex.
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Representative to Scientific Exhibit—Edwin Rayner Levine, Chicago.
Executive Committee—M. Jay Flipse, Miami, Fla.; Seymour M. Farber; Herman J. Moersch; Burgess L. Gordon; J. Winthrop Peabody Sr.

Tuesday, June 14—1:45 p. m.

FONTAINEBLEAU HOTEL, LA RONDE ROOM

BUSINESS MEETING

Chairman's Address: Clinical Appraisal of Pulmonary Cytology. Seymour M. Farber, San Francisco.

JOINT MEETING WITH THE SECTIONS ON GENERAL PRACTICE AND MILITARY MEDICINE

Tuesday, June 14—2 p. m.

FONTAINEBLEAU HOTEL, LA RONDE ROOM

PART I

Symposium on Medical Chest Emergencies

Effort, Occupation (including physicians) in Coronary Occlusion Arthur M. Master, New York.

Skin Diving Injuries, Predisposing Causes and Prevention.
Gerald J. Duffner, Washington, D. C.

Pulmonary Embolism. John F. Briggs, St. Paul.

Ventricular Difibrillation.
Lloyd D. MacLean and Robert A. vanTyn, St. Paul.

PART II

Laboratory and Clinical Studies of Cor Pulmonale Treated with the Newer Diuretics.
I. J. Greenblatt and A. Kahn, Brooklyn.

Sensitization to ACTH in Asthma.
Donald Lee Unger and Leon Unger, Chicago.

A Variant Form of Angina Pectoris.
Myron Prinzmetal, Hideo Toyoshima, Ali Ekmekci, and Teruo Nagaya, Los Angeles.

Surgical Management of Fungus Disease of the Lung.
Felix A. Hughes, Memphis, Tenn.

Wednesday, June 15—9 a. m.

FONTAINEBLEAU HOTEL, PASTEUR ROOM

JOINT MEETING WITH THE SECTIONS ON LARYNGOLOGY, OTOLOGY AND RHINOLOGY, AND RADIOLOGY

Panel Discussion on Tumors of the Trachea and Bronchial Tree

Moderator: Paul H. Holinger, Chicago

Endoscopist.
Herbert William Schmidt, Rochester, Minn.

Radiologists.
Barton R. Young, Philadelphia, and Wendell G. Scott, St. Louis.

Surgeons.
Robert J. Jensik, Chicago, and Robert W. Jamplis, Palo Alto, Calif.

Panel Discussion on Disseminated Diseases of the Chest

Moderator: Harold O. Peterson, Minneapolis

Internist. James A. Wier, Denver.
Chest Physician. David B. Radner, Chicago.
Endoscopist. Walter H. Maloney, Cleveland.

Radiologists.
Eugene F. Van Epps, Iowa City, and Clyde Alan Stevenson, Spokane, Wash.

Surgeons.
Donald L. Paulson, Dallas, Texas, and William M. Tuttle, Detroit.

Unusual Tumors of the Skin.
George C. Andrews and Anthony N. Domonkos, New York.

Wednesday, June 15—2 p. m.

DI LIDO HOTEL, COTILLION ROOM

ELECTION OF OFFICERS

Extramammary Paget's Disease—A Clinicopathologic Study.
Elson B. Helwig, Washington, D. C., and James H. Graham, Philadelphia.

Occlusive Dressings in Dermatology.
John Garb, New York.

Observations on the Bacteriology of an Outbreak of Staphylococcal Disease in a Dermatologic Service.
Laszlo Biro, Leon Buchbinder, Sidney Goldberg, Ottavio Pellitteri, and Richard C. Gibbs, New York.

Melkersson-Rosenthal Syndrome.
Samuel M. Bluefarb and Silas Wallk, Chicago.

Steroid Therapy of Dermatoses by the Vibrapuncture Technique.
William R. Vineyard, Robert S. Higdon, and James C. Lawler, Washington, D. C.

Lichen Sclerosus et Atrophicus—Are They the Same Disease? Richard A. Oberfield, Detroit.

Trends in Dermatological Office Practice.
David G. Welton, Charlotte, N. C.

Acanthosis Nigricans Associated with Metabolic Disease.
R. K. Winkelmann, S. R. Scheen, and L. O. Underdahl, Rochester, Minn.

Thursday, June 16—2 p. m.

DI LIDO HOTEL, COTILLION ROOM

Panel Discussion on Management of Fungus Infections

Moderator: J. Lamar Callaway, Durham, N. C.

Chemotherapy of *Fungus Infections.*
Harvey Blank, Miami, Fla.

Influence of Immunity on Treatment of Fungus Infections.
J. Walter Wilson, Los Angeles.

Treatment of Deep Fungus Infections.
E. Richard Harrell, Ann Arbor, Mich.

Treatment of *Superficial* Fungus Infections.
J. Fred Mullins, Galveston, Texas.

INSTALLATION OF OFFICERS

THE SOCIETY FOR INVESTIGATIVE DERMATOLOGY, INC.

OFFICERS

President—Thomas B. Fitzpatrick, Boston.
Vice-president—Harvey Blank, Miami, Fla.
Secretary-Treasurer—Herman Beerman, Philadelphia.

Program of The Society for Investigative Dermatology, Inc.

Monday, June 13—9 a. m.

DI LIDO HOTEL, COTILLION ROOM

Chairman: Thomas B. Fitzpatrick, Boston

Presidential Address: Clinical and Biochemical Studies of Human Albinism. Thomas B. Fitzpatrick, Boston.

The Reciprocal Relationship Between Melanization and Tyrosinase Activity in Melanin Granules.
Makoto Seiji and Thomas B. Fitzpatrick, Boston.

The Effect of Melatonin on Amphibian and Mammalian Melanocytes.
James D. Case and Aaron B. Lerner, New Haven, Conn.

Mechanisms of Migration of the Melanocytes from the Hair Follicle Into the Epidermis Following Dermabrasion.
Renato G. Staricco, Detroit.

Effect of Pregnancy on the Human Hair Cycle.
Yelva Lynfield, Chicago.

Histidine Metabolism in Urticaria Pigmentosa.
D. Joseph Demis, Washington, D. C., and Donald D. Brown, Bethesda, Md.

Quantitative Studies of Epidermal Sulfhydryl.
Ryohei Ogura, John M. Knox, and A. Clark Griffin, Houston, Texas.

Autoradiographic Studies of the Synthesis of Deoxyribonucleic Acid in the Skin of Young Rats.
Kimie Fukuyama and I. A. Bernstein, Ann Arbor, Mich.

Monday, June 13—2 p. m.

DI LIDO HOTEL, COTILLION ROOM

Studies on the Chemical Composition of Psoriatic Scales.
Victor R. Wheatley and Eugene M. Farber, Palo Alto, Calif.

Hyperuricemia and Psoriasis.
Robert R. Baumann and Otis F. Jillson, Hanover, N. H.

The Capillary Responses in Psoriatic Skin.
Paul Telner and Zoltan Fekete, Montreal, Canada.

Studies in Vascular Permeability of the Human Skin Using Coomassie Blue as Indicator.
Frederick Kalz and Zoltan Fekete, Montreal, Canada.

Vasomotor Studies in Ultraviolet Erythema.
Farrington Daniels Jr. and Lester Bergeron, Portland, Ore.

The Effect of Ultraviolet Light on Chemical Carcinogenesis.
John H. Epstein, Francis J. Sullivan, and William L. Epstein, San Francisco.

Studies of Dye Clearance and Eccrine Sweat Secretion in Human Skin.
Harry J. Hurley and Joseph A. Witkowski, Philadelphia.

The Effect of High and Low Salt Intake and Repeated Episodes of Sweating on the Human Eccrine Sweat Gland.
Richard L. Dobson, Donald C. Abele, and Dean M. Hale, Chapel Hill, N. C.

The Effect of Progesterone and Progesterone-Like Compounds on Human Sebaceous Glands.
John S. Strauss, Boston, and Albert M. Kligman, Philadelphia.

Tuesday, June 14—9 a. m.

DI LIDO HOTEL, COTILLION ROOM

Percutaneous Absorption of Nicotinic Acid and Analogs.
R. B. Stoughton, William Clendenning, and D. Kruse, Cleveland.

Diminished Effectiveness of the Epidermal Barrier of Intact Scrotal Skin.
J. Graham Smith Jr., Robert W. Fischer, and Harvey Blank, Miami, Fla.

Ileostomy and Colostomy.
John E. Ray and Merrell O. Hines, New Orleans.

Panel Discussion on Postsurgical Problems of the Gastrointestinal Tract

Moderator: Joseph B. Kirsner, Chicago

Participants: J. Alfred Rider, Thomas E. Machella, Maurice H. Stauffer, James Borland, Roy Hancock, John E. Ray, and Merrell O. Hines.

Wednesday, June 15—2 p. m.

FONTAINEBLEAU HOTEL, WEST BALLROOM

BUSINESS MEETING

Chairman's Address: Specialization and Gastroenterology.
Joseph B. Kirsner, Chicago.

Panel Discussion on Current Evaluation of Newer Diagnostic Procedures in Gastroenterology

The Current Status of Gastrointestinal Exfoliative Cytology.
Howard R. Raskin and Joseph B. Kirsner, Chicago.

Biopsies.
Benjamin H. Sullivan Jr., and John G. Batsakis, Washington, D. C.

Radioisotopes.
Julian M. Ruffin, Malcolm P. Tyor, Marion D. Hargrove Jr., and Richard R. Horswell, Durham, N. C.

Serum Enzymes.
Keith S. Henley, Ann Arbor, Mich.; Ellen Schmidt, and Fritz W. Schmidt, Kassel, Germany.

Panel Discussion on Drug-Induced Gastrointestinal Damage

Drug-Induced Damage to the Upper Gastrointestinal Tract.
Howard M. Spiro, New Haven.

Hepatic. Fenton Schaffner, New York.

Staphylococcic Enteritis.
William H. Dearing and Gerald M. Needham, Rochester, Minn.

Thursday, June 16—2 p. m.

FONTAINEBLEAU HOTEL, WEST BALLROOM

JOINT MEETING WITH THE SECTIONS ON PATHOLOGY, AND PHYSIOLOGY, RADIOLOGY, AND GENERAL SURGERY

Symposium on Current Status of Pancreatitis

Chairman: Champ Lyons, Birmingham, Ala., Chairman, Section on General Surgery.
Co-ordinating Secretary: G. Gordon McHardy, New Orleans, Secretary, Section on Gastroenterology and Proctology.

Pathologic Physiology of Pancreatic Inflammation.
David A. Dreiling, New York.

Evaluation of Newer Diagnostic Methods in Chronic Pancreatitis.
Harry Shay and David C. H. Sun, Philadelphia.

Newer Radiologic Investigations of the Pancreas.
Robert D. Moseley Jr., Chicago.

Medical Management of Pancreatitis.
Lloyd G. Bartholomew and James C. Cain, Rochester, Minn.

Surgical Aspects of Acute Pancreatitis.
John M. Howard, Philadelphia.

Surgical Treatment of Chronic Pancreatitis.
Henry Doubilet and John H. Mulholland, New York.

Panel Discussion on Current Status of Pancreatitis

Moderator: Edwin H. Ellison, Milwaukee.

Gastroenterology and Proctology.
Dwight L. Wilbur, San Francisco.

Pathology and Physiology.
Archie Baggenstoss, Rochester, Minn.

Radiology. William R. Eyler, Detroit.

Surgery. William J. Gillesby, Chicago.

SECTION ON GENERAL PRACTICE

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Secretary—Eugene I. Baumgartner, Oakland, Md.
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Representative to Scientific Exhibit—I. Phillips Frohman, Washington, D. C.
Executive Committee—S. A. Garlan, New York; Robert L. Crawford; Charles R. Alvey; Eugene I. Baumgartner; Lester D. Bibler.

Tuesday, June 14—2 p. m.

FONTAINEBLEAU HOTEL, LA RONDE ROOM

JOINT MEETING WITH THE SECTIONS ON DISEASES OF THE CHEST AND MILITARY MEDICINE

PART I

Symposium on Medical Chest Emergencies

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Donald Lee Unger and Leon Unger, Chicago.

A Variant Form of Angina Pectoris.
Myron Prinzmetal, Hideo Toyoshima, Ali Ekemekci, and Teruo Nagaya, Los Angeles.

Surgical Management of Fungus Disease of the Lung.
Felix A. Hughes, Memphis, Tenn.

Wednesday, June 15—8:45 a. m.

FONTAINEBLEAU HOTEL, EAST BALLROOM

BUSINESS MEETING; REPORT OF DELEGATE

Symposium on Edema—Its Physiology and Use of Newer Diuretics in its Treatment

Moderator: John H. Moyer, Philadelphia

SECTION ON EXPERIMENTAL MEDICINE AND THERAPEUTICS

OFFICERS OF SECTION

Chairman—Jack D. Myers, Pittsburgh.

Vice-chairman—Elliott V. Newman, Nashville, Tenn.

Secretary—Samuel P. Martin, Gainesville, Fla.

Delegate—Harry F. Dowling, Chicago.

Representative to Scientific Exhibit—Joseph F. Ross, Los Angeles.

Executive Committee—Charles H. Burnett, Chapel Hill, N. C.; Jack D. Myers; Elliott V. Newman; Samuel P. Martin; Harry F. Dowling.

Tuesday, June 14—2 p. m.

FONTAINEBLEAU HOTEL, EAST BALLROOM

JOINT MEETING WITH THE SECTION ON INTERNAL MEDICINE

Treatment of Shock with Sympathicomimetic Drugs—Use of Metaraminol and Comparison with Other Vasopressor Agents.
Lewis C. Mills, Ignatios J. Voudoukis, John H. Moyer, and Charles Heider, Philadelphia.
Discussion to be opened by George C. Morris Jr., Houston, Texas.

Induced Hypocalcemia and Its Effect Upon the Heart.
Alfred Soffer, Taft Y. Toribara, Dominic Moore-Jones, and Donald J. Weber, Rochester, N. Y.
Discussion to be opened by A. Raymond Terepka, Rochester, N. Y.

Latex Fixation Test, DNA-Protein Reaction and L. E. Cell Test Patterns of Reaction in Patients with Systemic Rheumatic Diseases.
Arthur P. Hall, Theodore B. Bayles, and Wadi A. Bardawil, Boston.
Discussion to be opened by David S. Howell, Miami, Fla.

Nervous and Muscular Systems in Myxedema: Clinical and Pathologic Study.
Stewart N. Nickel, Boy Frame, Jose Bebin, Detroit, and Wallace W. Tourtellotte, Ann Arbor, Mich.
Discussion to be opened by Kenneth R. Crispell, New York.

Symposium on Hypocholesteremic Drugs

Reduction of Hypercholesterolemia with Thyroid Analogues in the Brittle Coronary Patient.
Henry L. Jaffe, David W. Irving, and Eliot Corday, Los Angeles.

The Hypocholesteremic Effect of MER-29 (Triparanol) in Man. Arthur Ruskin, Galveston, Texas.

Inhibition of Cholesterol Synthesis by Triparanol.
Philip Lisan, Wilbur Oaks, and John H. Moyer, Philadelphia.

Reduction in Serum Cholesterol Levels and Other Metabolic Effects of Large Doses of Nicotinic Acid.
William B. Parsons Jr., Madison, Wis.
Discussion to be opened by Richard W. P. Achor, Rochester, Minn.

Wednesday, June 15—9 a. m.

FONTAINEBLEAU HOTEL, WEST BALLROOM

JOINT MEETING WITH THE SECTION ON NERVOUS AND MENTAL DISEASES

Panel Discussion on Psychopharmacology

Moderator: Samuel P. Martin, Gainesville, Fla.

Participants: Leo E. Hollister, Palo Alto, Calif.; Fritz Z. Freyhan, Farnhurst, Delaware; Jonathan Cole, Washington, D. C., and S. Bernard Wortis, New York.

Thursday, June 16—9 a. m.

FONTAINEBLEAU HOTEL, ROSEWOOD ROOM

BUSINESS MEETING

Chairman's Address. Jack D. Myers, Pittsburgh.

George Minot Lecture: The Control of Red Cell Production in Health and Disease. Leon O. Jacobson, Chicago.

Symposium on Organ Transplantation

Total Body Irradiation and Marrow Transplantation.
Joseph W. Ferrebee and E. Donnall Thomas, Cooperstown, N. Y.

Skin Transplantation. Blair O. Rogers, New York.

Organ Transplantation. Joseph E. Murray, Boston.

Intestinal Transplantation.
Richard C. Lillehei, Jerrold K. Longerbeam, Bernard Goott, Edmond Unis, and Sadek Hilal, Minneapolis.

SECTION ON GASTROENTEROLOGY AND PROCTOLOGY

OFFICERS OF SECTION

Chairman—Joseph B. Kirsner, Chicago.

Vice-chairman—William H. Dearing, Rochester, Minn.

Secretary—G. Gordon McHardy, New Orleans.

Delegate—Stuart T. Ross, Garden City, N. Y.

Representative to Scientific Exhibit—Willard Bernhoft, Buffalo, N. Y.

Executive Committee—A. W. Martin Marino, Brooklyn, N. Y.; Joseph B. Kirsner; William H. Dearing; G. Gordon McHardy; Stuart T. Ross.

Tuesday, June 14—2 p. m.

FONTAINEBLEAU HOTEL, WEST BALLROOM

Fatal Gastrointestinal Bleeding—An Analysis of 110 Deaths Occurring at Galveston, Texas in a Five-Year Period (1953-1957).
Marcel Patterson, Kenneth Weeden, and Eli Zonana, Galveston, Texas.

A Survey of the End-Results of Treatment of Carcinoma of the Stomach.
William F. Lipp and James F. Phillips, Buffalo, N. Y.

Symposium on Postsurgical Problems of the Gastrointestinal Tract

Esophageal Stricture and Esophagitis.
J. Alfred Rider and Hugo C. Moeller, San Francisco.

Gastric Resection Difficulties.
Thomas E. Machella, Philadelphia.

Complications of Vascular Shunts for Portal Hypertension.
Maurice H. Stauffer, Rochester, Minn.

Intestinal Resections and Anastomoses.
James Borland and Roy Hancock, Jacksonville, Fla.

The Hypocholesteremic Effect of MER-29 (Triparanol) in Man. Arthur Ruskin, Galveston, Texas.

Inhibition of Cholesterol Synthesis by Triparanol.
Philip Lisan, Wilbur Oaks, and John H. Moyer, Philadelphia.

Reduction in Serum Cholesterol Levels and Other Metabolic Effects of Large Doses of Nicotinic Acid.
William B. Parsons Jr., Madison, Wis.
Discussion to be opened by Richard W. P. Achor, Rochester, Minn.

Wednesday, June 15—2 p. m.

FONTAINEBLEAU HOTEL, EAST BALLROOM

ELECTION OF OFFICERS

Chairman's Address: Collagen Diseases—Some Unanswered Questions. Rudolph H. Kampmeier, Nashville, Tenn.

Comparative Survey of the Results of Treatment of 100 Cases of Bacterial Endocarditis.
Charles K. Friedberg, Hubert M. Goldman, Stuart R. Nemser and Leonard Field, New York.

Nephrogenic Polycythemia.
Robert K. Nixon and William O'Rourke, Detroit.

The Billings Lecture: Causality in Peptic Ulcer.
Walter L. Palmer, Chicago.

Subacute Cor Pulmonale—A Neglected Clinical Entity.
Maxwell L. Gelfand and Max Tesler, New York.

Ulcerative Colitis in Adolescence.
Robert P. Masland Jr., J. Roswell Gallagher, and W. Warren Point, Boston.

Thursday, June 16—2 p. m.

FONTAINEBLEAU HOTEL, EAST BALLROOM

JOINT MEETING WITH THE SECTION ON PREVENTIVE MEDICINE

Metabolic Changes Associated with Obesity Before and After Weight Reduction.
Donald Berkowitz and Nathaniel Berk, Philadelphia.

Disturbances of Carbohydrate Homeostasis.
John E. Potts, Walla Walla, Wash.; Mervin G. Hardinge, Geraldine M. Tupper, and Alma Will.
Discussion to be opened by Holbrooke Seltzer, Dallas Texas.

The Clinical Course of Patients with Orthostatic (Postural) Proteinuria. S. Edward King, New York.
Discussion to be opened by George James, New York.

Bacterial Endocarditis Following Dental Procedures of Cleaning and Filling of Teeth.
W. Proctor Harvey and Maurice A. Capone, Washington, D. C.
Discussion to be opened by John P. Utz, Bethesda, Md.

Toxoplasmosis Case Finding.
Fred Burford and W. D. Sutliff, Memphis, Tenn.

Diagnosis of Occult and Borderline Disorders of the Thyroid.
Edward N. Ehrlich and Richard L. Landau, Chicago.

Early Diagnosis and Differentiation of the Anemias.
Walter A. Rambach, Kenneth D. Kittleson and Howard L. Alt, Chicago.

A Radiological Health Survey on Diagnostic X-ray Equipment.
C. M. Sharp, J. O. Bond, E. G. Williams, and J. R. Knapp, Jacksonville, Fla.
Discussion to be opened by M. Eugene Flipse, Miami, Fla.

SECTION ON LARYNGOLOGY, OTOLOGY AND RHINOLOGY

OFFICERS OF SECTION

Chairman—Paul H. Holinger, Chicago.
Vice-Chairman—Lawrence R. Boies, Minneapolis.
Secretary—Walter E. Heck, San Francisco.
Delegate—Gordon F. Harkness, Davenport, Iowa.
Representative to Scientific Exhibit—Walter H. Maloney, Cleveland.
Executive Committee—Victor R. Alfaro, Washington, D. C.; Paul H. Holinger; Lawrence R. Boies; Walter E. Heck; Gordon F. Harkness.

Wednesday, June 15—9 a. m.

FONTAINEBLEAU HOTEL, PASTEUR ROOM

JOINT MEETING WITH THE SECTIONS ON DISEASES OF THE CHEST AND RADIOLOGY

Panel Discussion on Tumors of the Trachea and Bronchial Tree

Moderator: Paul H. Holinger, Chicago

Endoscopist.
Herbert William Schmidt, Rochester, Minn.

Radiologists.
Barton R. Young, Philadelphia, and Wendell G. Scott, St. Louis.

Surgeons.
Robert J. Jensik, Chicago, and Robert W. Jamplis, Palo Alto, Calif.

Panel Discussion on Disseminated Diseases of the Chest

Moderator: Harold O. Peterson, Minneapolis

Internist. James A. Wier, Denver.
Chest Physician. David B. Radner, Chicago.
Endoscopist. Walter H. Maloney, Cleveland.

Radiologists.
Eugene F. Van Epps, Iowa City, and Clyde Alan Stevenson, Spokane, Wash.

Surgeons.
Donald L. Paulson, Dallas, Texas, and William M. Tuttle, Detroit.

Thursday, June 16—9 a. m.

EDEN ROC HOTEL, PAVILION ROOM

Incidence of Hearing Impairment in a Medical Center Population.
Edmund P. Fowler Jr., and Thomas H. Fay, New York.

External Otitis: Specific Therapy Based on Accurate Diagnosis. Edley H. Jones, Vicksburg, Miss.

Address of Guest of Honor.
Louis H. Cierf, St. Petersburg, Fla.

Nasal Tip Surgery. Sam H. Sanders, Memphis, Tenn.

INTERMISSION

Address of Section Chairman.
Paul H. Holinger, Chicago.

Problems and Complications in Head and Neck Surgery.
George A. Sisson and Norman E. Johnson, Syracuse, N. Y.

The Long-Term Care of the Laryngectomized Patient.
George F. Reed, Boston.

Use of Diuretics in Diseases of the Kidney.
C. William Daeschner, Houston, Texas.

Use of Diuretics in Salt and Water Retention in Syndromes Due to Endocrine Abnormalities.
Garfield G. Duncan, Philadelphia.

Treatment of Heart Failure With Emphasis on the Use of Diuretics. Charles K. Friedberg, New York.

Clinical Pharmacology of Diuretics.
Morton Fuchs, Philadelphia.

Use of Diuretics in Hypertension.
Ray W. Gifford Jr., Rochester, Minn.

Chairman's Address: The Modern Family Physician.
Robert L. Crawford, Lancaster, S. C.

Symposium on Newer Trends in Therapy

Earlier Administration of Oxygen for Acute Coronary Thrombosis, Including a Discussion of Patient Applied Oxygen Inhalation for Coronary Insufficiency.
Alvan L. Barach, New York.

The Use of Pancreatic Dornase in the Lysis of Pulmonary and Laryngeal Secretions.
Robert G. Chambers, Baltimore.

The Use of Silicones in the Treatment of Intestinal Gas and Bloating. J. Alfred Rider, San Francisco.

Newer Trends in the Feeding of Infants.
Walter W. Sackett, Miami, Fla.

Thursday, June 16–8:45 a. m.

FONTAINEBLEAU HOTEL, EAST BALLROOM

BUSINESS MEETING; ELECTION OF OFFICERS

Symposium on Pathogenesis and Treatment of Thrombo-embolic Phenomena

Moderator: Irving S. Wright, New York

General Consideration of Modern Therapy of Thrombo-embolic Diseases. Irving S. Wright, New York.

General Clinical Experiences.
Eugene E. Cliffton, New York.

Basic Biochemical Characteristics and Nature of the Fibrinolytic System. Julian L. Ambrus, Buffalo, N. Y.

Surgical Aspects of Thrombo-embolic Phenomena.
William G. Anlyan, Durham, S. C.

Laboratory Procedures and Therapy in Coronary Emboli.
Paul W. Boyles, Miami Beach, Fla.

Symposium on Newer Trends in Diagnosis and Treatment

Oxygen: The Rational Therapy for Systemic Toxic Reactions from Local Anesthetic Drugs.
Daniel C. Moore and L. Donald Bridenbaugh, Seattle.

Diagnosis and Treatment of Cervical Disc Disease.
George W. Smith, Augusta, Ga.

Newer Concepts of Amine Oxidase Inhibitors.
Arthur L. Scherbel, Cleveland.

The Stethoscopic Audibility of Sounds.
Dale Groom, Charleston, S. C.

Friday, June 17–9 a. m.

FONTAINEBLEAU HOTEL, EAST BALLROOM

JOINT MEETING WITH THE SECTION ON PHYSICAL MEDICINE

This will be a demonstration type of meeting. There will be presentation of patients with discussion of care in certain entities commonly seen in older age groups. The general subjects will be:

Cerebral Vascular Accidents

Early Care. Edward D. Haak, Warm Springs, Ga.

Physical Rehabilitation.
William C. Fleming, Coral Gables, Fla.

Speech Rehabilitation.
Josephine Simonson, Rochester, Minn.

New Developments in the Fitting and Rehabilitation of Amputees

A Demonstration With Emphasis on the Geriatric Amputee.
Ralph E. Worden, Los Angeles.

Arthritis

Rheumatoid Arthritis and Osteoarthritis.
Edward W. Lowman, New York.

Surgical Treatment of the Rheumatoid Hand.
Edward D. Henderson, Rochester, Minn.

SECTION ON INTERNAL MEDICINE

OFFICERS OF SECTION

Chairman—Rudolph H. Kampmeier, Nashville, Tenn.
Vice-chairman—George T. Harrell Jr., Gainesville, Fla.
Secretary—Wright R. Adams, Chicago.
Delegate—Charles T. Stone Sr., Galveston, Texas.
Representative to Scientific Exhibit—Henry T. Ricketts, Chicago.
Executive Committee—William B. Bean, Iowa City; Rudolph H. Kampmeier; George T. Harrell Jr.; Wright R. Adams; Charles T. Stone Sr.

Tuesday, June 14–2 p. m.

FONTAINEBLEAU HOTEL, EAST BALLROOM

JOINT MEETING WITH THE SECTION ON EXPERIMENTAL MEDICINE AND THERAPEUTICS

Treatment of Shock with Sympathicomimetic Drugs: Use of Metaraminol and Comparison with Other Vasopressor Agents.
Lewis C. Mills, Ignatios J. Voudoukis, John H. Moyer, and Charles Heider, Philadelphia.
Discussion to be opened by George C. Morris Jr., Houston, Texas.

Induced Hypocalcemia and Its Effect Upon the Heart.
Alfred Soffer, Taft Y. Toribara, Dominic Moore-Jones, and Donald J. Weber, Rochester, N. Y.
Discussion to be opened by A. Raymond Terepka, Rochester, N. Y.

Latex Fixation Test, DNA-Protein Reaction and L. E. Cell Test Patterns of Reaction in Patients with Systemic Rheumatic Diseases.
Arthur P. Hall, Theodore B. Bayles, and Wadi A. Bardawil, Boston.
Discussion to be opened by David S. Howell, Miami, Fla.

Nervous and Muscular Systems in Myxedema: Clinical and Pathologic Study.
Stewart N. Nickel, Boy Frame, Jose Bebin, Detroit, and Wallace W. Tourtellotte, Ann Arbor, Mich.
Discussion to be opened by Kenneth R. Crispell, New York.

Symposium on Hypocholesteremic Drugs

Reduction of Hypercholesterolemia with Thyroid Analogues in the Brittle Coronary Patient.
Henry L. Jaffe, David W. Irving, and Eliot Corday, Los Angeles.

SECTION ON MISCELLANEOUS TOPICS

Session on Allergy

OFFICERS OF SECTION

Co-chairmen—Cecil M. Kohn, Kansas City, Mo.
Francis C. Lowell, Boston.
Secretary—Jack A. Rudolph, Miami Shores, Fla.

Tuesday, June 14—2 p. m.

FONTAINEBLEAU HOTEL, ROSEWOOD ROOM

Allergy in Every Day Medical Practice.
Lawrence J. Halpin, Cedar Rapids, Iowa.
Diagnosis: Allergy and Infection of the Respiratory Tract.
Burton M. Rudolph and Jack A. Rudolph, Miami Shores, Fla.

Panel Discussion on Asthma in Children and Adults

Moderator: Leon Unger, Chicago.

Participants: Susan C. Dees, Durham, N. C., Jerome Glaser, Rochester, N. Y., and Joseph H. Shaffer, Detroit.

INTERMISSION

Drug Allergy, Mechanism: Diagnosis and Treatment.
Alexander A. Fisher, Woodside, L. I., N. Y.
Research in Allergy and Progress Being Made.
William B. Sherman, New York.

Panel Discussion on Dyspnea

Moderator: Harvey E. Brown Jr., Coral Gables, Fla.

Participants: George L. Baum, Charles W. Silverblatt, and Mark Wolcott, Coral Gables, and Morris Dressler, Miami, Fla.

Question and answer period.

Session on Aging

OFFICERS OF SESSION

Chairman—Frederick C. Swartz, Lansing, Mich.
Secretary—Edward H. Williams, Miami, Fla.

Wednesday, June 15—2 p. m.

FONTAINEBLEAU HOTEL, FRENCH ROOM

Symposium on Management of the Older Patient

Current Concepts of the Aging Process.
Nathan W. Shock, Baltimore.
Maintenance of Activity. Michael M. Dacso, New York.
Risks and Results of Surgery. Philip Thorek, Chicago.
Medical Management.
Wingate M. Johnson, Winston-Salem, N. C.
Psychiatric Management.
Ewald W. Busse and John B. Reckless, Durham, N. C.

SECTION ON NERVOUS AND MENTAL DISEASES

OFFICERS OF SECTION

Chairman—E. S. Gurdjian, Detroit.
Vice-chairman—William T. Lhamon, Houston, Texas.
Secretary—Howard P. Rome, Rochester, Minn.
Delegate—Francis M. Forster, Madison, Wis.
Representative to Scientific Exhibit—Benjamin Boshes, Chicago.
Executive Committee—Kenneth E. Appel, Philadelphia; E. S. Gurdjian; William T. Lhamon; Howard P. Rome; Francis M. Forster.

Wednesday, June 15—9 a. m.

FONTAINEBLEAU HOTEL, WEST BALLROOM

JOINT MEETING WITH THE SECTION ON EXPERIMENTAL MEDICINE AND THERAPEUTICS

Panel Discussion on Psychopharmacology

Moderator: Samuel P. Martin, Gainesville, Fla.

Participants: Leo E. Hollister, Palo Alto, Calif.; Fritz A. Freyhan, Farnhurst, Del.; Jonathan Cole, Washington, D. C., and S. Bernard Wortis, New York.

Wednesday, June 15—1:30 p. m.

FONTAINEBLEAU HOTEL, ROSEWOOD ROOM

BUSINESS MEETING

Chairman's Address: Critique of Occlusive Disease of the Carotid Artery and the Stroke Syndrome.
E. S. Gurdjian, Detroit.
Hemodynamic Consideration in the Diagnosis and Treatment of the Cerebral Stroke.
Eliot Corday and Sanford Rothenberg, Los Angeles.
Prevention of Degenerative Disease: A Controlled Study of Anticoagulant Prophylaxis.
J. R. Whittier, C. D. Korenyi, D. F. Klein, and W. Foley, New York.
Evaluation of Methyl Lysergic Acid Butanolamide (UML 491) in the Treatment of Vascular Headaches.
Arnold P. Friedman and Sheldon Losin, New York.
Some Psychological Aspects of Histaminic Cephalgia.
Richard M. Steinhilber and John S. Pearson, Rochester, Minn.
Cervical Spondylosis.
William W. Anderson, Burton L. Wise, and H. H. Itabashi, San Francisco.

Thursday, June 16—9 a. m.

FONTAINEBLEAU HOTEL, ROSEWOOD ROOM

Reality Distortion and Neurotic Behavior in Isolation.
Robert L. Vosburg, Pittsburgh.
The Significance of the Gamma-globulin Fraction in Multiple Sclerosis and Other Neurologic Diseases, Based on Cerebrospinal Fluid Paper Strip Electrophoretic Patterns of 594 Patients.
N. P. Goldstein, R. R. Ivers, B. F. McKenzie, and W. F. McGuckin, Rochester, Minn.
Rupture of the Neural Tube: The Cause of Myelomeningocele. W. James Gardner, Cleveland.
Some Observations About Patients With a Breast Mass.
Max Sugar and Charles Watkins, New Orleans.
Psychopharmacology and the "Deteriorated" Schizophrenic Patients.
Sidney V. Cohen and Ruth M. Pillsbury, Los Angeles.
Hunger and Satiety. Albert T. Stunkard, New York.

Thursday, June 16—2 p. m.

FONTAINEBLEAU HOTEL, ROSEWOOD ROOM

Comments on the Relations Between Psychiatrists and Other Physicians. Leo H. Bartemeier, Baltimore.

BUSINESS MEETING

Report of Section Delegate and Alternate.
Gordon F. Harkness, Davenport, Iowa, and Dean M. Lierle, Iowa City.

Report of Section Representatives to Board of Governors of the American College of Surgeons.
Edley H. Jones, Vicksburg, Miss., John J. Conley, New York, and Harold Owens, Los Angeles.

Report of Nominations Committee.
Alden H. Miller, Los Angeles, Chairman; Fletcher D. Woodward, Charlottesville, Va., and George A. Sisson, Syracuse, N. Y.

ELECTION OF OFFICERS AND NOMINATION OF REPRESENTATIVES TO BOARD OF GOVERNORS OF THE AMERICAN COLLEGE OF SURGEONS

Luncheon honoring Louis H. Clerf, Section Guest of Honor.

Friday, June 17—9 a. m.

EDEN ROC HOTEL, PAVILION ROOM

Cystadenoma of the Parotid and of the Larynx (Case Reports). Arthur J. Kuhn, Hammond, Ind.

Effect of Premarin on the Ground Substance.
Maurice Schiff, Oak Knoll, Calif., and Helen E. Burn, San Francisco.

Cervico-Facial Congenital Anomalies.
Richard T. Farrior, Tampa, Fla.

Audiology: Its Progress and Problems.
Kenneth O. Johnson, Washington, D. C.

Otometric Operations.
George D. Albers, Grand Rapids, Mich.

INTERMISSION

Five Year Results of Stapes Mobilization and Current Results with Vein Plug Stapedeoplasty.
C. M. Kos, Iowa City.

Fenestration of the Oval Window.
John T. Shea Jr., Memphis, Tenn.

Use of Ear Canal Skin in Myringoplasty.
William F. House, Los Angeles.

Problems with Tympanoplasty.
Edward C. Brandow Jr., Albany, N. Y.

SECTION ON MILITARY MEDICINE

OFFICERS OF SECTION

Chairman—George H. Houck, Palo Alto, Calif.
Vice-chairman—James H. Kidder, Washington, D. C.
Secretary—James T. McGibony, Washington, D. C.
Delegate—Alphonse McMahon, St. Louis, Mo.
Representative to Scientific Exhibit—Frank M. Townsend, Washington, D. C.
Executive Committee—Alphonse McMahon, St. Louis; George H. Houck; James H. Kidder; James T. McGibony.

Tuesday, June 14—2 p. m.

FONTAINEBLEAU HOTEL, LA RONDE ROOM

JOINT MEETING WITH THE SECTIONS ON DISEASES OF THE CHEST AND GENERAL PRACTICE

PART I

Symposium on Medical Chest Emergencies

Effort, Occupation (including physicians) in Coronary Occlusion. Arthur M. Master, New York.

Skin Diving Injuries, Predisposing Causes and Prevention.
Gerald J. Duffner, Washington, D. C.

Pulmonary Embolism. John F. Briggs, St. Paul.

Ventricular Defibrillation.
Lloyd D. MacLean and Robert A. vanTyn, St. Paul.

PART II

Laboratory *and Clinical Studies* of Cor Pulmonale Treated with Newer Diuretics.
I. J. Greenblatt and A. Kahn, Brooklyn.

Sensitization to ACTH in Asthma.
Donald Lee Unger and Leon Unger, Chicago.

A Variant Form of Angina Pectoris.
Myron Prinzmetal, Hideo Toyoshima, Ali Ekmekci, and Teruo Nagaya, Los Angeles.

Surgical Management of Fungus Disease of the Lung.
Felix A. Hughes, Memphis, Tenn.

Wednesday, June 15—9 a. m.

EDEN ROC HOTEL, POMPEII ROOM

BUSINESS MEETING; ELECTION OF OFFICERS

Chairman's Address: *Total Medicine—A Challenge to Military and Civilian Physicians.*
George H. Houck, Palo Alto, Calif.

Symposium on the Medical Importance of Chemical, Biological and Radiological Warfare

Moderator: Leonard D. Heaton, Washington, D. C.

Medical Aspects of Chemical Warfare.
Van M. Sim, Army Chemical Center, Md.

The *Physician's* Role in the Defense Against Biological Warfare.
Dan Crozier, Washington, D. C., William D. Tigertt, Fort Detrick, Md., and Joseph W. Cooch, Washington, D. C.

Radiological Warfare: *Care of the Individual Patient.*
Carl L. Hansen, Rochester, N. Y.

A Look to the Future.
J. H. McNinch, Washington, D. C.

Discussion to be opened by B. W. Hogan, and L. K. Niess, Washington, D. C.

Thursday, June 16—9 a. m.

EDEN ROC HOTEL, POMPEII ROOM

Activities of the Office of the Assistant Secretary of Defense (Health and Medical) During the Past Year.
Frank B. Berry, Washington, D. C.

Evaluation of Incision and Suction in Snakebite Therapy.
T. W. Merriam Jr. and R. S. Leopold, Camp Lejeune, N. C.

Stress or Fatigue Fractures of the Femur, Tibia, Fibula, Calcaneus and Metatarsal of Marine Recruits.
Ralph W. Geise and Daniel J. Engen, Beaufort, S. C.

Reiter's Syndrome: Factors in Diagnosis and Treatment.
Raymond Scalettar and Darrell C. Crain, Washington, D. C.

Experiences in the Treatment of Acquired Mitral Valve Disease Using Open Heart Techniques.
Dean F. Winn Jr., Clarence L. Anderson, Herbert E. Reese, Denver, and John M. Salyer, Santa Ana, Calif.

The Military Significance of Partial Gastrectomy—Report of 500 Cases. Philip D. Cronemiller, San Diego, Calif.

Electroretinography in Pediatric Ophthalmology.
George Goodman, and Harris Ripps, New York.
Discussion to be opened by Herman M. Burian, Iowa City.

A Study of Pulseless Disease.
Joseph L. Dowling Jr., Providence, R. I., and Taylor R. Smith, Boston.
Discussion to be opened by Victor Curtin, Miami, Fla.

Wednesday, June 15—1:30 p. m.

EDEN ROC HOTEL, MONA LISA ROOM

EXECUTIVE SESSION

Visual Field Changes Following Temporal Lobectomy.
John Wendland, and Sidney Nerenberg, Minneapolis.
Discussion to be opened by C. Wilbur Rucker, Rochester, Minn.

Opsoclonus. J. Lawton Smith, Baltimore.
Discussion to be opened by Edward W. D. Norton, Miami, Fla.

Contact Lenses for Aphakics.
Robert C. Welsh, Miami, Fla.

Acute Complication from Modern Corneal Contact Lenses: A Report of 14 New Cases.
Richard K. Lansche, and Robert Lee, Munich.
Discussion to be opened by Elizabeth Constantine, New York.

Recent Experiences with Light Coagulation.
Herbert Wiesinger, Walter Geeraets, and Du Pont Guerry III, Richmond, Va.
Discussion by William H. Havener, Columbus, Ohio, and Taylor R. Smith, Boston.

Thursday, June 16—1:30 p. m.

EDEN ROC HOTEL, MONA LISA ROOM

Recent Advances in Ocular Surgery

Chairman's Address. Harold G. Scheie, Philadelphia.

Address of Guest of Honor: Enzymatic Zonulolysis in Lens Extraction. Joaquin Babbaquer, Barcelona, Spain.
Discussion to be opened by Derrick T. Vail, Chicago.

Address of Invited Foreign Guest: Anterior Chamber Lenses —Present Operative Technique.
Benedetto Strampelli, Rome, Italy.

Address of Invited Foreign Guest: Uses of Anterior Chamber Implants in Ocular Surgery.
D. P. Choyce, London, England.
Discussion by Joaquin Barraquer, Barcelona, Spain, and Du Pont Guerry III, Richmond, Va.

Surgical Treatment of Bullous Keratopathy.
Trygve Gundersen, Boston.
Discussion to be opened by A. Edward Maumenee, Baltimore.

Surgical Treatment of Epithelial Cysts of the Anterior Chamber.
Ernest K. Goodner and Michael J. Hogan, San Francisco.
Discussion to be opened by Paul A. Chandler, Boston.

A Report on 42 Cases of Glaucoma Treated by Peripheral Iridectomy with Scleral Cautery.
George S. Tyner, Duane Lahey, John Elliff, and Harry Watts, Denver.
Discussion by John M. McLean, New York, and Carteret Lawrence, Baltimore.

ASSOCIATION FOR RESEARCH IN OPHTHALMOLOGY, INC.

Twenty-Ninth Annual Session

OFFICERS

Chairman—James H. Allen, New Orleans.
Secretary-Treasurer—Lorand V. Johnson, Cleveland.

Program of Association for Research in Ophthalmology, Inc.

Monday, June 13—8:45 a. m.

EDEN ROC HOTEL, MONA LISA ROOM

Presiding: James H. Allen, New Orleans

The Measurement of Rabbit Ciliary Epithelial Potentials In Vitro.
James E. Miller and Marguerite A. Constant, St. Louis.
Discussion to be opened by Albert M. Potts.

The Transport of Organic Anions by the Rabbit Ciliary Body: I. In Vitro Iodopyracet (Diodrast Accumulation).
Bernard Becker, St. Louis.
Discussion to be opened by V. Everett Kinsey.

The Transport of Organic Anions by the Rabbit Ciliary Body: II. In Vivo Transport of Iodopyracet (Diodrast).
Max Forbes and Bernard Becker, St. Louis.
Discussion to be opened by V. Everett Kinsey.

Diabetic Retinopathy.
J. Reimer Wolter, Ann Arbor, Mich.
Discussion to be opened by B. S. Fine.

INTERMISSION

The Morphology of the Vitreous Body.
B. S. Fine and A. J. Tousimis, Washington, D. C.
Discussion to be opened by George K. Smelser.

Visual Pigment Concentration and the Electroretinogram.
John E. Dowling, Cambridge, Mass.
Discussion to be opened by Werner K. Noell.

The Role of Macular Function in the ERG of Monkey and Man.
J. H. Jacobson, H. T. Najac and G. F. Gestring, New York.
Discussion to be opened by A. D. Ruedemann Jr.

Experimental Malignant Melanoma of the Iris in the Syrian Golden Hamster.
Robert P. Burns and F. Fraunfelder, Portland, Ore.
Discussion to be opened by John S. McGavic.

Tuesday, June 14—9 a. m.

EDEN ROC HOTEL, MONA LISA ROOM

Observations on Experimental Trachoma Produced in Cynamolgus Monkeys by Elementary Body Virus Strains Propagated in Volk Sac.
P. Thygeson, D. Dawson, L. Hanna, and M. Okumoto, San Francisco.
Discussion to be opened by Alson E. Braley.

The Effect of Corticosteroids on Acute Experimental Ocular Toxoplasmosis. Herbert E. Kaufman, Boston.
Discussion to be opened by Ralph W. Ryan.

Corneal Destruction of Extracts of Cephalosporium Mycelium. C. D. Burda and E. Fisher Jr., New Orleans.
Discussion to be opened by Albert P. Ley.

New Horizons in Psychiatric Hospitalization.
Lauren H. Smith, Philadelphia.

Are Medical Students Learning Psychiatry?
R. H. Greenbank, Upper Darby, Pa.

Eugenic Sterilization. Morton Birnbaum, Brooklyn, N. Y.

Clinical Study of Hyperthyroidism.
Austin W. Bennett and Charles Glenn Cambor, Pittsburgh.

Elipten: A New Anticonvulsant.
Frederic T. Zimmerman, New York.

SECTION ON OBSTETRICS AND GYNECOLOGY

OFFICERS OF SECTION

Chairman—Curtis J. Lund, Rochester, N. Y.
Vice-chairman—H. Close Hesseltine, Chicago.
Secretary—Keith P. Russell, Los Angeles.
Delegate—Ralph E. Campbell, Madison, Wis.
Representative to Scientific Exhibit—Frederick H. Falls, River Forest, Ill.
Executive Committee—Nicholson J. Eastman, Baltimore; Curtis J. Lund; H. Close Hesseltine; Keith P. Russell; Ralph E. Campbell.

Tuesday, June 14—2 p. m.

MIAMI BEACH EXHIBITION HALL, ROOM A

Chairman's Address. Curtis J. Lund, Rochester, N. Y.

Factors Influencing the Ratio of Uterine Cancer: A Relative Study in Two Baltimore Hospitals.
Edmund R. Novak and Umberto Villa Santa, Baltimore.

Detection of Gynecologic Cancer by Fluorescence Microscopy. Walter Sussman, Philadelphia.

Discussion of papers by Drs. Novak and Sussman.

Electron Microscopy of Renal Biopsies in Toxemia of Pregnancy.
Albert Altchek, W. Mautner, Jacob Churg, and Edith Grishman, New York.

The Use of Syntocinon in Nursing or Non-Nursing Mothers: Its Effect on Lactation and Uterine Involution.
Robert H. Stewart, Seattle.

Use of Intranasal Oxytocin in Obstetrics.
Charles H. Hendricks and S. V. Pose, Cleveland.

Discussion of papers by Drs. Stewart and Hendricks.

BUSINESS MEETING

Wednesday, June 15—2 p. m.

MIAMI BEACH EXHIBITION HALL, ROOM A

JOINT MEETING WITH THE SECTIONS ON ANESTHESIOLOGY, PATHOLOGY AND PHYSIOLOGY, AND GENERAL SURGERY

Symposium on Operating Room Fatalities

Moderator: Henry K. Beecher, Boston

Introduction. Henry K. Beecher, Boston.
Surgical Aspects. Curtis P. Artz, Jackson, Miss.
Obstetrical and Gynecological Aspects.
James H. Ferguson, Miami, Fla.
Anesthesiologist's Viewpoint. Jay Jacoby, Miami, Fla.
Pathologist's Viewpoint. Milton Helpern, New York.
Panel Discussion.

Thursday, June 16—2 p. m.

MIAMI BEACH EXHIBITION HALL, ROOM A

Cardiac Arrest in Obstetrics: Experience in New York City 1959.
Edwin M. Gold, Harold Jacobziner, and Jean Pakter, New York.

31,595 Deliveries With One Maternal Death.
Stirling G. Pillsbury, Long Beach, Calif.

An Answer for Criminal Abortion.
Jerome M. Kummer, Santa Monica, Calif., and Zad Leavy, Los Angeles.

Discussion of papers by Drs. Gold, Pillsbury, and Kummer.

Experience in a *Vaginitis* Clinic.
Warren R. Lang, Philadelphia.

An Embryologic Derived Classification of Ovarian Tumors.
Milton L. Bassis, San Francisco.

The Management of Varicose Veins of Pregnancy.
Robert A. Nabatoff, New York.

Discussion of papers by Drs. Lang, Bassis, and Nabatoff.

SECTION ON OPHTHALMOLOGY

SECTION OFFICERS

Chairman—Harold G. Scheie, Philadelphia.
Vice-chairman—Paul A. Chandler, Boston.
Secretary—Henry F. Allen, Boston.
Delegate—Ralph O. Rychener, Memphis, Tenn.
Representative to Scientific Exhibit—Frank W. Newell, Chicago.
Executive Committee—Frank B. Walsh, Baltimore; Harold G. Scheie; Paul A. Chandler; Henry F. Allen; Ralph O. Rychener.

Program of Section on Ophthalmology

Tuesday, June 14—1:30 p. m.

EDEN ROC HOTEL, MONA LISA ROOM

The Selection of Operative Procedures in Vertical Muscle Imbalances. Edward A. Dunlap, New York.

Vertical Recti Transplantation in the A and V-Syndromes.
James E. Miller, St. Louis.

Discussion by Philip Knapp, New York, and Charles F. *Cooper* Jr., Atlanta, Ga.

Ultrasonography: An Aid in Orbital Tumor Diagnosis.
Gilbert Baum, Bronx, New York.

Discussion to be *opened* by Elmer J. Ballintine, Cleveland.

Granuloma as a Complication of Polyethylene Tube Buckling Procedures for Retinal Detachment.
Harvey Lincoff, New York.

Discussion to be opened by Silvio von Pirquet, *Boston.*

Precancerous Epithelioma of the Limbus.
Frank C. Winter and Thomas R. Kleh, *Palo Alto*, Calif.

Discussion to be opened by John S. McGavic, Bryn Mawr, Pa.

Pathology of Ocular Leprosy. I. Cornea.
James H. Allen, New Orleans, and *Jerome* L. Byers, Dallas.

Discussion to be opened by D. P. Choyce, London, England.

Surgery of the Arthritic Hand.
Lee Ramsey Straub, New York.

Surgical Demonstration.
Lester A. Russin and William S. Weinkle, Miami Beach, Fla.

Lesions Simulating Rheumatoid Arthritis in the Joints of the Hands and Feet.
J. Leonard Goldner, Durham, N. C.

Rheumatoid Factor. Richard H. Freyberg, New York.

Wednesday, June 15—2 p. m.

FONTAINEBLEAU HOTEL, FONTAINE ROOM

Surgical Fixation of Small but Important Bone Fragments with the Hookplate; Review of a Method Used in the Last Ten Years in About 450 Cases (Mainly Involving Joint Fractures of the Ankle and Elbow.)
Wilhelm A. Zuelzer, Fort Belvoir, Va.
Discussion to be opened by Joseph Homer Dimon III, Boston.

Traumatic Sciatic Palsy in Premature Infants; Report and Follow-up Study of Ten Cases.
Paul H. Curtiss Jr., and Howard J. Tucker, Cleveland.
Discussion to be opened by Charles R. Burbacher, Coral Gables, Fla.

An End-Result Study of Congenital Clubfeet Treated at the Alfred I. duPont Institute.
A. R. Shands Jr., and G. Dean MacEwen, Wilmington, Del., and Daniel J. Scott Jr., Portsmouth, Va.
Discussion to be opened by Joseph Hiram Kite, Atlanta, Ga.

The Infant's Hip—Normal or "Dysplastic"?
Charles T. Ryder, John Caffey, and Gilbert Mellin, New York.
Discussion to be opened by Paul Pemberton, Salt Lake City.

Surgery of the Extremities in the Treatment of Cerebral Palsy. Sidney Keats, Newark, N. J.
Discussion to be opened by Tom Outland, Harrisburg, Pa.

An Acetabular Replacement Prosthesis—Five Year Follow-up Report. Earl D. McBride, Oklahoma City.
Discussion to be opened by Fredeick G. Gaenslen, Milwaukee.

Intertrochanteric Fractures: Factors Governing the Roentgenographic Prognosis and Complications of Nailing.
Augusto Sarmiento, Miami, Fla.
Discussion to be opened by Leonard T. Peterson, Washington, D. C.

BUSINESS MEETING

Second Executive Session.
Election of Officers.

Thursday, June 16—2 p. m.

FONTAINEBLEAU HOTEL, FONTAINE ROOM

Supracondylar Fractures in Children.
William J. Mitchell and John P. Adams, Washington, D. C.
Discussion to be opened by Jack Hughston, Columbus, Ga.

Diagnosis and Treatment of Bone Tumors in Children.
Spencer A. Rowland, C. Roger Sullivan, David C. Dahlin, and Alvin B. Hayles, Rochester, Minn.
Discussion to be opened by William F. Enneking, Gainesville, Fla.

The Differential Diagnosis of Isolated Bone Lesions Containing Giant Cells. James I. Kendrick, Cleveland.
Discussion to be opened by Edward D. Henderson, Rochester, Minn.

Chairman's Address. H. Herman Young, Rochester, Minn.

The Management of Complicated Ununited Fractures of the Tibia and Fibula. H. R. McCarroll, St. Louis.
Discussion to be opened by Arthur H. Weiland, Coral Gables, Fla.

Motion Picture: Surgical Repair of the Ligaments of the Knee and Ankles in Acute Injuries.
Leslie M. Bodnar, South Bend, Ind., and Joseph B. Crowley, Notre Dame, Ind.
Discussion to be opened by Charles J. Frankel, Charlottesville, Va.

SECTION ON PATHOLOGY AND PHYSIOLOGY

OFFICERS OF SECTION

Chairman—Russell L. Holman, New Orleans.
Vice-Chairman—Lester R. Dragstedt, Chicago.
Secretary—Hugh A. Edmondson, Los Angeles.
Delegate—Lall G. Montgomery, Muncie, Ind.
Representative to Scientific Exhibit—Samuel A. Levinson, Chicago.
Executive Committee—Thomas M. Peery, Washington, D. C.; Russell L. Holman; Lester R. Dragstedt; Hugh A. Edmondson; Lall G. Montgomery.

Tuesday, June 14—2 p. m.

EDEN ROC HOTEL, POMPEII ROOM

BUSINESS MEETING

Chairman's Address. Russell L. Holman, New Orleans.

Viral Etiology of Lymphomas.
Joseph W. Beard, Durham, N. C.

Histologic Diagnostic and Prognostic Features in Malignant Lymphomas.
George J. Hummer, Santa Monica, Calif.

The Simulation of Malignant Lymphomas by Benign Proliferative Processes of Lymphoid Tissue.
Robert J. Lukes, Washington, D. C.

Lymphomas of the G. I. Tract. John W. Berg, New York.

The Diagnosis of Lymphomas Involving the Skin.
Elson B. Helwig, Washington, D. C.

Chemotherapy of Malignant Lymphomas.
Henry D. Diamond, New York.

Wednesday, June 15—2 p. m.

MIAMI BEACH EXHIBITION HALL, ROOM A

JOINT MEETING WITH THE SECTIONS ON ANESTHESIOLOGY, OBSTETRICS AND GYNECOLOGY, AND GENERAL SURGERY

Symposium on Operating Room Fatalities

Moderator: Henry K. Beecher, Boston

Introduction. Henry K. Beecher, Boston.

Surgical Aspects. Curtis P. Artz, Jackson, Miss.

Obstetrical and Gynecological Aspects.
James H. Ferguson, Miami, Fla.

Anesthesiologist's Viewpoint. Jay Jacoby, Milwaukee.

Pathologist's Viewpoint. Milton Helpern, New York.

Panel Discussion

Studies on Experimental Ocular Drug Hypersensitivity.
A. M. SILVERSTEIN, S. WELTER, and L. E. ZIMMERMAN, Washington, D. C.
Discussion to be opened by PHILLIPS THYGESON.

BUSINESS SESSION

INTERMISSION

The Rapid and Convenient Detection of Toxoplasma Antibodies Using Formalized Human Red Cells.
HERBERT E. KAUFMAN, Boston.
Discussion to be opened by SEYMOUR P. HALBERT.

The Regulation of the Intraocular Pressure in the Cat's Eye.
MAURICE E. LANGHAM, Baltimore.
Discussion to be opened by LUDWIG VON SALLMANN.

The Scleral Rigidity Function.
M. G. HOLLAND, J. MADISON, and W. BEAN, New Orleans.
Discussion to be opened by E. J. BALLINTINE.

Wednesday, June 15—9 a. m.

EDEN ROC HOTEL, MONA LISA ROOM

Nutritional and Endocrine Influences on the Synthesis of Albuminoid in Rat Lenses: II. The Effect of Pituitary Hormones and of Testosterone on the Albuminoid Synthesis in Rat Lenses.
ZACHARIAS DISCHE and GINEVRA ZELMENIS, New York.
Discussion to be opened by P. J. LEINFELDER.

Resolution of Phenol Sulfokinase and Phenol Sulfatase in Beef Cornea by Cellulose Anion Exchanger. Chromatography.
B. WORTMAN and A. SCHNEIDER, St. Louis.
Discussion to be opened by J. WINSTON BARBER.

The Effect of Oxygen Tension on Glucose Uptake by the Isolated Rabbit Lens.
R. P. LEWIS, Portland, Ore.; J. E. HARRIS, Minneapolis, and E. L. TALMAN, Portland, Ore.
Discussion to be opened by CARL WACHTL.

***Photosensitization of Proteins* by Methylene Blue: II. Alteration of Malic and Lactic Dehydrogenase Activity of Rabbit Lenses.** W. L. FOWLKS, Minneapolis.
Discussion to be opened by MARGUERITE A. CONSTANT.

INTERMISSION

On the Evolution of Lens Proteins.
W. MANSKI, S. P. HALBERT, and T. AUERBACH, New York.
Discussion to be opened by CARL WACHTL.

A Critique of Time Amplitude Ultrasonography.
GILBERT BAUM, Bronx, New York.

PROCTOR MEDAL RECIPIENT: SIR STEWART DUKE-ELDER

Thursday, June 16—9 a. m.

EDEN ROC HOTEL, MONA LISA ROOM

Effect of Plasma on Glucose Uptake by Isolated Rat Lenses.
T. G. FARKAS, R. F. IVORY, S. J. COOPERSTEIN, Cleveland, and J. W. PATTERSON, Nashville, Tenn.
Discussion to be opened by D. VENKAT REDDY.

Content and Distribution of Ribonucleic Acid in Rat Lenses in Relation to Age and Cataract Formation.
ANIMA DEVI and ZACHARIAS DISCHE, New York.
Discussion to be opened by JOHN F. R. KUCK JR.

Further Studies on Corneal Transparency.
ALBERT M. POTTS, Chicago, and B. FRIEDMAN, Cleveland.
Discussion to be opened by JOHN E. HARRIS.

The Effect of Endothelium on Corneal Wound Healing—Experimental Study. JAMES E. MCDONALD, Chicago.
Discussion to be opened by FREDERICK W. STOCKER.

INTERMISSION

The Ultrastructure of Bowman's Membrane.
JACK KAYES and AKE HOLMBERT, St. Louis
Discussion to be opened by GEORGE D. PAPPAS.

The Enigma of Typical Monochromacy.
MATHEW ALPERN and HAROLD F. FALLS, Ann Arbor Mich.
Discussion to be opened by GORDON L. WALLS.

FRIEDENWALD MEMORIAL LECTURE—IRVING H. LEOPOLD

SECTION ON ORTHOPEDIC SURGERY

OFFICERS OF SECTION

Chairman—H. HERMAN YOUNG, Rochester, Minn.
Vice-Chairman—JAMES VERNON LUCK, Los Angeles.
Secretary—ROBERT J. JOPLIN, Brookline, Mass.
Assistant Secretary—JOHN C. WILSON JR., Los Angeles.
Delegate—EDWARD L. COMPERE, Chicago.
Representative to Scientific Exhibit—JAMES I. KENDRICK Cleveland.
Assistant Representative to Scientific Exhibit—ERNEST BURKE EVANS, Galveston, Texas.

Tuesday, June 14—1 p. m.

FONTAINEBLEAU HOTEL, FONTAINE ROOM

Shoulder Arthrography.
ROBERT L. SAMILSON, San Francisco
Discussion to be opened by GRAHAM A. KERNWEIN Rockford, Ill.

Skeletal Anomalies Associated with Myelomeningocele and Syringomyelia.
W. JAMES GARDNER and JOHN S. COLLIS, Cleveland
Discussion to be opened by JAMES W. HARKESS Augusta, Ga.

Diastematomyelia With Acquired Clubfoot Deformity.
CLYDE W. DAWSON, Columbus, Ohio
Discussion to be opened by JOHN C. WILSON JR., Lo Angeles.

Congenital Plantar Flexed Talus (Congenital Dislocation of the Talo Navicular Joint).
FREDERICK S. CRAIG, New York
Discussion to be opened by JAMES VERNON LUCK, Lo Angeles.

BUSINESS MEETING

First Executive Session.
Report from Delegate: EDWARD L. COMPERE, Chicago.
New Business.

Tuesday, June 14—3:15 p. m.

MIAMI BEACH AUDITORIUM, ROOM D

The following program has been coordinated with the Color Television program which will be presented in the Miami Beach Auditorium, Room D. The telecast, sponsored and produced by Smith, Kline & French Laboratories of Philadelphia, will originated from the Mount Sinai Hospital.

Surgical Aspects of Rheumatoid Arthritis and Lesions Similating Rheumatoid Arthritis

Moderator: EDWARD W. CULLIPHER, Miami

Pulmonary Abnormalities in Congenital Heart Disease.
LULU M. HAROUTUNIAN and CATHERINE A. NEILL, Baltimore.

Surgical Emergencies in the Newborn.
WILLIAM R. RICHARDSON, Oklahoma City.

SECTION ON PHYSICAL MEDICINE

OFFICERS OF SECTION

Chairman—LEWIS A. LEAVITT, Houston, Texas.
Vice-Chairman—JAMES W. RAE JR., Ann Arbor, Mich.
Secretary—EARL C. ELKINS, Rochester, Minn.
Delegate—WALTER J. ZEITER, Cleveland.
Representative to Scientific Exhibit—RALPH E. WORDEN, Los Angeles.
Executive Committee—ARTHUR L. WATKINS, Boston; LEWIS A. LEAVITT; JAMES W. RAE JR; EARL C. ELKINS; WALTER J. ZEITER.

Wednesday, June 15—9 a. m.

FONTAINEBLEAU HOTEL, FRENCH ROOM

BUSINESS MEETING

Chairman's Address: Frontiers of Physical Medicine and Rehabilitation. LEWIS A. LEAVITT, Houston, Texas.

Electromyographic Method for Objective Measurement of Muscle Relaxant Drugs.
CHARLES R. PETERSON and CHARLES S. WISE, Washington, D. C.

Physical Medicine and Rehabilitation: Dynamic Results in Chronic Illness and Aging.
A. B. C. KNUDSON, Washington, D. C.

The Challenge of Disability to Medicine.
CHARLES D. SHIELDS and BERNARD D. DAITZ, Washington, D. C.

Management of Spinal Cord Injuries at the Elizabeth Kenny Institute. JOSEPH P. ENGEL, Minneapolis.

The Evaluation Process in Rehabilitation Center Inpatients.
CARL LEVENSON and WILLIAM J. ERDMAN II, Philadelphia.

Care Program Requirements of a County Hospital Population.
EDWIN M. SMITH and JAMES W. RAE JR., Ann Arbor, Mich.

Thursday, June 16—9 a. m.

JOINT MEETING WITH THE SECTION ON PEDIATRICS

FONTAINEBLEAU HOTEL, FONTAINE ROOM

Symposium on Cerebral and Spinal Cord Lesions in Children

Cerebral Lesions in Infancy: Limitations of Present Neurologic Examination Techniques.
PAUL M. ELLWOOD JR., Minneapolis.

Physical Rehabilitation of Spinal Cord Lesions in Children.
HAROLD M. STERLING, Brighton, Mass.

Physical Rehabilitation of the Child with Cerebral Lesion.
PHOEBE SATUREN and JEROME S. TOBIS, New York.

The Challenge of the Emotional Needs of Children with Central Nervous System Lesions.
ARR NELL BOELSCHE, Galveston, Texas.

Ambulation Problems in Very Young Children.
ERNEST W. JOHNSON, Columbus, Ohio.

Symposium on Rheumatoid Arthritis as a Cause of Chronic Disability in Children

Diagnosis in Juvenile Rheumatoid Arthritis.
EDWARD F. ROSENBERG, Chicago.

Physical Medicine and Rehabilitation for Arthritis in Children. MILAND E. KNAPP, Minneapolis.

Abuse of Therapeutic Measures in Rheumatoid Arthritis in Children.
GUNNAR B. STICKLER and JOHN G. MAYNE, Rochester, Minn.

Friday, June 17—9 a. m.

FONTAINEBLEAU HOTEL, EAST BALLROOM

JOINT MEETING WITH THE SECTION ON GENERAL PRACTICE

This will be a demonstration type of meeting. There will be presentation of patients with discussion of care in certain entities commonly seen in older age groups. The general subjects will be:

Cerebral Vascular Accidents

Early Care. EDWARD D. HAAK, Warm Springs, Ga.

Physical Rehabilitation.
WILLIAM C. FLEMING, Coral Gables, Fla.

Speech Rehabilitation.
JOSEPHINE SIMONSON, Rochester, Minn.

New Developments in the Fitting and Rehabilitation of Amputees

A Demonstration With Emphasis on the Geriatric Amputee.
RALPH E. WORDEN, Los Angeles.

Arthritis

Rheumatoid Arthritis and Osteoarthritis.
EDWARD W. LOWMAN, New York.

Surgical Treatment of the Rheumatoid Hand.
EDWARD D. HENDERSON, Rochester, Minn.

SECTION ON PREVENTIVE MEDICINE

OFFICERS OF SECTION

Chairman—WILFORD F. HALL, Dayton, Ohio.
Vice-chairman—WILSON T. SOWDER, Jacksonville, Fla.
Secretary—LEMUEL C. MCGEE, Wilmington, Del.
Delegate—RUTHERFORD T. JOHNSTONE, Los Angeles.
Representative to Scientific Exhibit—PAUL A. DAVIS, Akron, Ohio.
Executive Committee—ROBERT A. KEHOE, Cincinnati; WILFORD F. HALL; WILSON T. SOWDER; LEMUEL C. MCGEE; RUTHERFORD T. JOHNSTONE.

Tuesday, June 14—2 p. m.

EDEN ROC HOTEL, PAVILION ROOM

BUSINESS MEETING

Medical Aspects of Safety in the Air.
JAN H. TILLISCH, Rochester, Minn.

Developments in Aerospace Medicine and the Association with Preventive Medicine.
OTIS O. BENSON, Brooks Air Force Base, Texas.

Air Travel and the Cardiopulmonary Patient—Motion Picture.
ROBERT B. STONEHILL, San Antonio, Texas.

Thursday, June 16—2 p. m.

FONTAINEBLEAU HOTEL, WEST BALLROOM

JOINT MEETING WITH THE SECTIONS ON GASTROENTEROLOGY AND PROCTOLOGY, RADIOLOGY, AND GENERAL SURGERY

Symposium on Current Status of Pancreatitis

Chairman: CHAMP LYONS, Birmingham, Ala., Chairman, Section on General Surgery.

Co-ordinating Secretary: G. GORDON MCHARDY, New Orleans, Secretary, Section on Gastroenterology and Proctology.

Pathologic Physiology of Pancreatic Inflammation.
DAVID A. DREILING, New York.

Evaluation of Newer Diagnostic Methods in Chronic Pancreatitis.
HARRY SHAY and DAVID C. H. SUN, Philadelphia.

Newer Radiologic Investigations of the Pancreas.
ROBERT D. MOSELEY JR., Chicago.

Medical Management of Pancreatitis.
LLOYD G. BARTHOLOMEW and JAMES C. CAIN, Rochester, Minn.

Surgical Aspects of Acute Pancreatitis.
JOHN M. HOWARD, Philadelphia.

Surgical Treatment of Chronic Pancreatitis.
HENRY DOUBILET and JOHN H. MULHOLLAND, New York.

Panel Discussion on Current Status of Pancreatitis

Moderator: EDWIN H. ELLISON, Milwaukee

Gastroenterology and Proctology.
DWIGHT L. WILBUR, San Francisco.

Pathology and Physiology.
ARCHIE BAGGENSTOSS, Rochester, Minn.

Radiology. WILLIAM R. EYLER, Detroit.

Surgery. WILLIAM J. GILLESBY, Chicago.

SECTION ON PEDIATRICS

OFFICERS OF SECTION

Chairman—CLEMENT A. SMITH, Boston.

Vice-Chairman—ROBERT GRAYSON, Miami Beach, Fla.

Secretary—ARILD E. HANSEN, Oakland, Calif.

Delegate—WALTER B. STEWART, Atlantic City, N. J.

Representative to Scientific Exhibit—F. THOMAS MITCHELL, Memphis, Tenn.

Executive Committee—WYMAN C. C. COLE SR., Detroit; CLEMENT A. SMITH; ROBERT GRAYSON; ARILD E. HANSEN; WALTER B. STEWART.

Wednesday, June 15—9 a. m.

FONTAINEBLEAU HOTEL, FONTAINE ROOM

BUSINESS MEETING

Report on Abraham Jacobi Fund.
HUGH L. DWYER, Kansas City, Mo.

Chairman's Address. CLEMENT A. SMITH, Boston.

Present Knowledge of Human Congenital Anomalies.
VIRGINIA APGAR, New York.

The Protein Requirement in Infancy and Childhood.
JOSEPH A. JOHNSTON, MICHAEL JAMES SWEENEY, RICHARD BROWN, GORDON MANSON, and JOHN WALKER MAHONEY, Detroit.

Symposium on Congenital Heart Disease: Present Day Status from Viewpoint of the Practitioner of Medicine

Moderator: LEONARD S. SOMMER, Miami, Fla.

Pediatric Cardiologist. CATHERINE NEILL, Baltimore.

Roentgenologist. ROBERT N. COOLEY, Galveston, Texas.

Anesthesiologist. KENNETH K. KEOWN, Columbia, Mo.

Surgeon. JOHN R. DERRICK, Galveston, Texas.

Thursday, June 16—9 a. m.

FONTAINEBLEAU HOTEL, FONTAINE ROOM

JOINT MEETING WITH THE SECTION ON PHYSICAL MEDICINE

Symposium on Cerebral and Spinal Cord Lesions in Children

Cerebral Lesions in Infancy: Limitations of Present Neurologic Examination Techniques.
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GUNNAR B. STICKLER and JOHN G. MAYNE, Rochester, Minn.

Friday, June 17—9 a. m.

FONTAINEBLEAU HOTEL, FONTAINE ROOM

Children and the Post-Concussion Syndrome.
HAROLD DILLON and ROBERT L. LEOPOLD, Philadelphia.

Polio Problems from Viewpoint of Practitioner.
E. RUSSELL ALEXANDER and ALEXANDER D. LANGMUIR, Atlanta, Ga.

Infectious Hepatitis in Children.
ROBERT WARD, Los Angeles, SAUL KRUGMAN, and JOAN P. GILES, New York.

Management of the Child with Diabetes Mellitus.
ROBERT L. JACKSON, Columbia, Mo.

Management of Child with Nephrosis.
KURT LANGE, EDWARD WASSERMAN, and LAWRENCE SLOBODY, New York.

Treatment of Reticuloendotheliosis with Corticosteroids and Antifolic Acid Compounds.
PAUL FREUD, New York.

Bilateral Herniorrhapy in Infants and Children.
MICHEL GILBERT, Miami, Fla.

Surgical Treatment of Ulcerative Colitis in Children.
KENNETH C. SAWYER, ROBERT B. SAWYER, and ROBERT E. MCCURDY, Denver.

Pulmonary Abnormalities in Congenital Heart Disease.
Lulu M. Haroutunian and Catherine A. Neill, Baltimore.

Surgical Emergencies in the Newborn.
William R. Richardson, Oklahoma City.

SECTION ON PHYSICAL MEDICINE

OFFICERS OF SECTION

Chairman—Lewis A. Leavitt, Houston, Texas.
Vice-Chairman—James W. Rae Jr., Ann Arbor, Mich.
Secretary—Earl C. Elkins, Rochester, Minn.
Delegate—Walter J. Zeiter, Cleveland.
Representative to Scientific Exhibit—Ralph E. Worden, Los Angeles.
Executive Committee—Arthur L. Watkins, Boston; Lewis A. Leavitt; James W. Rae Jr; Earl C. Elkins; Walter J. Zeiter.

Wednesday, June 15—9 a. m.

FONTAINEBLEAU HOTEL, FRENCH ROOM

BUSINESS MEETING

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The Evaluation Process in Rehabilitation Center Inpatients.
Carl Levenson and William J. Erdman II, Philadelphia.

Care Program Requirements of a County Hospital Population.
Edwin M. Smith and James W. Rae Jr., Ann Arbor, Mich.

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FONTAINEBLEAU HOTEL, FONTAINE ROOM

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Paul M. Ellwood Jr., Minneapolis.

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Harold M. Sterling, Brighton, Mass.

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Gunnar B. Stickler and John G. Mayne, Rochester, Minn.

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Arthritis

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Edward W. Lowman, New York.

Surgical Treatment of the Rheumatoid Hand.
Edward D. Henderson, Rochester, Minn.

SECTION ON PREVENTIVE MEDICINE

OFFICERS OF SECTION

Chairman—Wilford F. Hall, Dayton, Ohio.
Vice-chairman—Wilson T. Sowder, Jacksonville, Fla.
Secretary—Lemuel C. McGee, Wilmington, Del.
Delegate—Rutherford T. Johnstone, Los Angeles.
Representative to Scientific Exhibit—Paul A. Davis, Akron, Ohio.
Executive Committee—Robert A. Kehoe, Cincinnati; Wilford F. Hall; Wilson T. Sowder; Lemuel C. McGee; Rutherford T. Johnstone.

Tuesday, June 14—2 p. m.

EDEN ROC HOTEL, PAVILION ROOM

BUSINESS MEETING

Medical Aspects of Safety in the Air.
Jan H. Tillisch, Rochester, Minn.

Developments in Aerospace Medicine and the Association with Preventive Medicine.
Otis O. Benson, Brooks Air Force Base, Texas.

Air Travel and the Cardiopulmonary Patient—Motion Picture.
Robert B. Stonehill, San Antonio, Texas.

Wednesday, June 15—2 p. m.

EDEN ROC HOTEL, PAVILION ROOM

The Role of the International Cooperation Administration in International Health.
Eugene P. Campbell, Washington, D. C.

Standards for Occupational Health Services.
James P. Hughes, Oakland, Calif.

The Advantages of Administration of Governmentally Operated Health and Medical Programs by a Medically Directed Agency Rather Than by a Non-Medically Directed Agency. Ben Freedman, New Orleans.
Discussion to be opened by Phineas J. Sparer, Memphis, Tenn.

The Epidemiology and Prevention of Childhood Accidents.
Harold Jacobziner, Herbert Rich, and Roland Merchant, New York.

Regulatory Problems and Radiation Hazards.
Melvin M. Udel, New York.

Mental Retardation: Medical and Public Health Aspects.
Franklin M. Foote, Hartford, Conn.

Thursday, June 16—2 p. m.

JOINT MEETING WITH THE SECTION ON INTERNAL MEDICINE

FONTAINEBLEAU HOTEL, EAST BALLROOM

Metabolic Changes Associated with Obesity Before and After Weight Reduction.
Donald Berkowitz and Nathaniel Berk, Philadelphia.

Disturbances of Carbohydrate Homeostasis.
John E. Potts, Walla Walla, Wash.; Mervyn G. Hardinge, Geraldine M. Tupper and Alma Will.
Discussion to be opened by Holbrooke Seltzer, Dallas, Texas.

The Clinical Course of Patients with Orthostatic (Postural) Proteinuria. S. Edward King, New York.
Discussion to be opened by George James, New York.

Bacterial Endocarditis Following Dental Procedures of Cleaning and Filling of Teeth.
W. Proctor Harvey and Maurice A. Capone, Washington, D. C.
Discussion to be opened by John P. Utz, Bethesda, Md.

Toxoplasmosis Case Finding.
Fred Burford and W. D. Sutliff, Memphis, Tenn.

Diagnosis of Occult and Borderline Disorders of the Thyroid.
Edward N. Ehrlich and Richard L. Landau, Chicago.

Early Diagnosis and Differentiation of the Anemias.
Walter A. Rambach, Kenneth D. Kittleson, and Howard L. Alt, Chicago.

A Radiological Health Survey on Diagnostic X-ray Equipment.
C. M. Sharp, J. O. Bond, E. G. Williams, and J. R. Knapp, Jacksonville, Fla.
Discussion to be opened by M. Eugene Flipse, Miami.

SECTION ON RADIOLOGY

OFFICERS OF SECTION

Chairman—Sydney F. Thomas, Palo Alto, Calif.

Vice-chairman—J. Paul Medelman, St. Paul.

Secretary—Traian Leucutia, Detroit.

Delegate—Eugene P. Pendergrass, Philadelphia.

Representative to Scientific Exhibit—Richard H. Chamberlain, Philadelphia.

Executive Committee—Ted F. Leigh, Atlanta, Ga.; Sydn F. Thomas; J. Paul Medelman; Traian Leucut Eugene P. Pendergrass.

Wednesday, June 15—9 a. m.

FONTAINEBLEAU HOTEL, PASTEUR ROOM

JOINT MEETING WITH THE SECTIONS ON DISEASES OF TH CHEST AND LARYNGOLOGY, OTOLOGY AND RHINOLOGY

Moderator: Paul H. Holinger, Chicago

Endoscopist.
Herbert William Schmidt, Rochester, Mi

Radiologists.
Barton R. Young, Philadelphia and Wendell Scott, St. Louis.

Surgeons.
Robert J. Jensik, Chicago and Robert W. Jampl Palo Alto, Calif.

Panel Discussion on Disseminated Diseases of the Chest

Moderator: Harold O. Peterson, Minneapolis

Internist. James A. Wier, Denv

Chest Physician. David B. Radner, Chica

Endoscopist. Walter H. Maloney, Clevela

Radiologists.
Eugene V. Van Epps, Iowa City, and Clyde Al Stevenson, Spokane, Wash.

Surgeons.
Donald L. Paulson, Dallas, Texas, and William Tuttle, Detroit.

Thursday, June 16—9 a. m.

FONTAINEBLEAU HOTEL, PASTEUR ROOM

ELECTION OF OFFICERS

Chairman's Address: Radiation: A Chemical.
Sydney F. Thomas, Palo Alto, Cal

Roentgenologic Manifestations of Non-Infectious Arthri in Small Bones and Joints.
Russell F. Scalf and Ji-toong Ling, Louisville, K

Angiographic Diagnosis of Traumatic Head and Ne Lesions.
John A. Campbell and Robert L. Campbel Indianapolis.

Penetrating Wounds of the Chest.
Vincent P. Collins and Carroll A. Peabody, Hou ton, Texas.

Scintillating Scanning in the Differential Diagnosis of Thor co-Abdominal Midline Masses.
Frederick J. Bonte, J. S. Krohmer, C. H. Tseng, ar M. C. L. Baldwin, Dallas, Texas.

The Radiologic Aspects of Pyloric Channel Ulcer.
A. W. Sommer, D. N. Dysart, and R. D. Haine Temple, Texas.

Radiologic Observations in Cases of Fistulas of the Bilia Tract. W. H. Shehadi, New Yor

Extrarectal Tumors Caused by *Silent Carcinomas* of th Stomach and Pancreas.
Julian O. Salik, Baltimor

Neoplasms of the Kidney: A Radiologic Study.
John A. Evans, New York

Voiding: Its Muscular Requirements.
Ahmad Hatam, Robert Lich Jr., Lonnie W. Hower ton, and Everett L. Pirkey, Louisville, Ky.

Carcinoma of the Kidney.
Edward N. Cook, Rochester, Minn.

Diagnosis and Treatment of Urinary Tract Infection in Children. Ralph A. Straffon, Cleveland.

Three Years' Experience With Ureteral Reimplantation and Bladder Neck Reconstruction.
Guy W. Leadbetter Jr., Boston.

Changing Concepts in the Diagnosis of Lower Urinary Tract Obstruction in Children.
Frank C. Hamm and Keith Waterhouse, Brooklyn, N. Y.

The Value of Delayed Cystography.
A. Waite Bohne, Richard D. Urwiller, and Donald F. Armento, Detroit.

COLOR TELEVISION

MIAMI BEACH AUDITORIUM, ROOM D

The program has been prepared by the following Local Committee on Television:

Richard M. Fleming, Miami, Chairman.
Joseph T. Jana, Miami.
Leon H. Manheimer, Miami Beach.
David A. Nathan, Miami Beach.
Don W. Smith, Miami.
Franz H. Stewart, Miami.

The telecasts, sponsored and produced by Smith, Kline & French Laboratories, Inc., of Philadelphia, will originate from the Mount Sinai Hospital.

Monday, June 13—2 p. m.

Some Old and Some New Techniques in the Differential Diagnosis of Jaundice

Moderator: Winston K. Shorey, Miami.

Participants: Richard C. Clay, Fredie P. Gargano, Miami, and Allan Kaplan, Miami Beach.

Operating Surgeons: Richard M. Fleming, Miami, and Leon H. Manheimer, Miami Beach.

Modern Diagnostic Cardiovascular Techniques

Moderator: Victor H. Kugel, Miami Beach.

Participants: Philip Samet, Miami Beach, Francisco A. Hernandez, William P. Murphy Jr., Leonard S. Sommer, Miami, and Jack Widrich, Miami Beach.

Tuesday, June 14—10 a. m.

Correlative Clinics on Problems of Aging

Moderator: John Baxter Liebler, Miami.

Participants: Francis N. Cooke, Samuel Gertman, and Malcolm Ross, Miami.

Poisoning—Types and Management

Moderator: Robert B. Lawson, Miami.

Participants: Robert Grayson, William B. Deichmann, John T. Kilpatrick, and W. E. Haast, Miami.

Tuesday, June 14—2 p. m.

Misery in Paradise—A Consideration of Certain Rheumatoid Problems Encountered in Florida

Moderator: J. F. Keeley Jr., Miami.

Participants: Phyllis Vaughn, Harvey Brown, David Howell, and Allen C. De Olazarra, Miami.

Surgical Aspects of Rheumatoid Arthritis and Lesions Simulating Rheumatoid Arthritis

Moderator: Edward W. Cullipher, Miami.

Surgery of the Arthritic Hand.
Lee Ramsey Straub, New York.

Surgical Demonstration.
Lester A. Russin and William S. Weinkle, Miami Beach.

Lesions Simulating Rheumatoid Arthritis in the Joints of the Hands and Feet.
J. Leonard Goldner, Durham, N. C.

Rheumatoid Factor. Richard H. Freyberg, New York.

Wednesday, June 15—10 a. m.

Skin Manifestations of Systemic Disease

Moderator: Lewis Capland, Miami Beach.

Participants: Wiley Sams and Harvey Blank, Miami.

Regional Perfusion

Moderator: Daniel S. Martin, Miami.

Panelists: Joseph Aust, Minneapolis, Jacob Colsky, Miami, Oscar Creech Jr., New Orleans, Frederick Golomb, Frederic Herter, New York, and John Stehlin, Houston.

Surgeons: Daniel S. Martin, George Prout, Augustus Sarmiento, and H. M. White Jr., Miami.

Wednesday, June 15—2 p. m.

Radioactive Isotopes—Their Contribution to Definite Diagnosis and Treatment

Moderator: Robert E. Bauer, Miami Beach.

Participants: Frank Kurzweg, Ray Parks, Miami, Jacob Neber and Allan Kaplan, Miami Beach.

Cardiac Arrest—Prevention and Treatment

Moderator: David A. Nathan, Miami Beach.

Participants: J. Gerard Converse, Louis Lemberg, De Witt C. Daughtry, Miami, and Hugh Stevenson, Columbia, Mo.

Thursday, June 16—10 a. m.

Crime and Medicine

Moderator: Franklin J. Evans, Miami.

Participants: Joseph H. Davis, Ray H. Pearson, and Richard E. Gerstein, Miami.

Anticoagulants and Fibrinolysins

Moderator: Robert J. Boucek, Miami.

Participants: E. Sterling Nichol, Ralph Jones Jr., Julian L. Ambrus, and Morton M. Halpern, Miami.

Thursday, June 16—2 p. m.

Peptic Ulcer: Basis for Present Treatment and A Look To The Future

Moderator: Donald F. Marion, Miami.

Participants: Emil Isberg, John J. Farrell, Edward Woodward, Miami, and Robert J. Priest, Detroit.

Operation for Duodenal Ulcer

Surgeons: Walter C. Jones Jr. and L. W. Dowlen, Miami.

So-called Unexplained Operating Room Infections: The Source and a Method of Control by Use of Ultraviolet Radiation.
Deryl Hart, Durham, N. C.

The Place for Antibiotics in Surgical Patients.
Edwin J. Pulaski, Fort Dix, N. J.

Regional *Perfusion with Antibiotics in the Treatment of* Chronic Infections.
R. F. Ryan, Keith Reemtsma, G. W. Beddingfield, Oscar Creech Jr., and J. K. Wickstrom, New Orleans.

Medical Illustration—℞ for Use.
Robert H. Albertin, Milwaukee.

Panel Discussion on The Treatment of Specific Infections in the Surgical Patient

Moderator: John M. Waugh, Rochester, Minn.

Treatment of Generalized Peritonitis.
James D. Hardy, Jackon, Miss.

Staphylococcus Pneumonia and Septicemia.
Peter Dineen, New York.

Parotitis, Enterocolitis, Septicemia in General.
Claude E. Welch, Albany, N. Y.

Septicophlebitis, Suppurative Lymphadenitis, General Problems Including the Infected Burned Patient.
John J. Farrell, Miami, Fla.

Furuncles, Carbuncles, and Cellulitis—Localized Abscess of the Peritoneal Cavity. Leo M. Zimmerman, Chicago.

Thursday, June 16—2 p. m.

FONTAINEBLEAU HOTEL, WEST BALLROOM

JOINT MEETING WITH THE SECTIONS ON GASTROENTEROLOGY AND PROCTOLOGY, PATHOLOGY AND PHYSIOLOGY, AND RADIOLOGY

Symposium on Current Status of Pancreatitis

Chairman: Champ Lyons, Birmingham, Ala., Chairman, Section on General Surgery.

Co-ordinating Secretary: G. Gordon McHardy, New Orleans, Secretary, Section on Gastroenterology and Proctology.

Pathologic Physiology of Pancreatic Inflammation.
David A. Dreiling, New York.

Evaluation of Newer Diagnostic Methods in Chronic Pancreatitis.
Harry Shay and David C. H. Sun, Philadelphia.

Newer Radiologic Investigations of the Pancreas.
Robert D. Moseley Jr., Chicago.

Medical Management of Pancreatitis.
Lloyd G. Bartholomew and James C. Cain, Rochester, Minn.

Surgical Aspects of Acute Pancreatitis.
John M. Howard, Philadelphia.

Surgical Treatment of Chronic Pancreatitis.
Henry Doubilet and John H. Mulholland, New York.

Panel Discussion on Current Status of Pancreatitis

Moderator: Edwin H. Ellison, Milwaukee.

Gastroenterology and Proctology.
Dwight L. Wilbur, San Francisco.

Pathology and Physiology.
Archie Baggenstoss, Rochester, Minn.

Radiology.
William R. Eyler, Detroit.

Surgery.
William J. Gillesby, Chicago.

SECTION ON UROLOGY

OFFICERS OF SECTION

Chairman—Thomas A. Morrissey, New York.
Vice-Chairman—Harry Spence, Dallas, Texas.
Secretary—Edward H. Ray, Lexington, Ky.
Assistant Secretary—Myron Nourse, Indianapolis.
Delegate—Jay J. Crane, Los Angeles.
Representative to Scientific Exhibit—E. F. Poutasse, Cleveland.
Assistant Representative to Scientific Exhibit—Dean Parker, Seattle.
Executive Committee—Milton M. Coplan, Miami, Fla.; Thomas A. Morrissey; Harry Spence; Edward H. Ray; Jay J. Crane.

Tuesday, June 14—2 p. m.

FONTAINEBLEAU HOTEL, PASTEUR ROOM

The Perineal Prostatectomy: A Modified Young Technique for Conservative Enucleations.
Jasper H. Arnold, Houston, Texas.

Chronic, Idiopathic Retroperitoneal Fibrosis.
John K. Ormond, Dale R. Drew, and Kenneth L. Urwiller, Detroit.

Triacetyloleandomycin with Triple Sulfa: Its Role in the Control of Staphylococcus and Streptococcus Infections *in the Urinary Tract.*
Grayson Carroll, Dinos Gibas, and D. Karellos, St. Louis.

The Renal Transport of Nitrofurantoin and the Effect of Acid-Base Balance Upon Its Excretion.
Marvin W. Woodruff, Richard L. Malvin, and Ian M. Thompson, Ann Arbor, Mich.

The Prevention and Management of Surgical Injuries to the Ureter: *With Emphasis on Early Repair.*
Harry M. Spence and Ted Boone, Dallas.

The Diagnosis of Bladder Outlet Obstruction.
John J. Murphy and Harry W. Schoenberg, Philadelphia.

Wednesday, June 15—2 p. m.

FONTAINEBLEAU HOTEL, PASTEUR ROOM

The Use of Fine Polyethylene Tubing as a Splint in Anastomosis of the Vas Deferens.
Stanwood S. Schmidt, Eureka, Calif.

Antispermatozoal Immunologic Factors in the Etiology of Infertility.
Edward T. Tyler, Henry J. Olson, M. Gotlib, Shanta Rao, Sheldon Segal, and N. Nakabayashi, Los Angeles.

Chairman's Address. Thomas A. Morrissey, New York.

A Method for Selecting Those Hypertensive Patients With Urological Etiology, Who Will Be Cured by Surgery.
Chester C. Winter, Los Angeles.

Mechanism and Treatment of Stress Incontinence.
Jack Lapides, Edward P. Ajemian, Bruce H. Stewart, John R. Lichtwardt, and Barry A. Breakey, Ann Arbor, Mich.

BUSINESS *MEETING; ELECTION OF OFFICERS*

Thursday, June 16—2 p. m.

FONTAINEBLEAU HOTEL, PASTEUR ROOM

Carcinoma of the Prostate: Comparison of Immediate With Delayed Endocrine Therapy.
R. Theodore Bergman, Henry L. Hadley and Douglas Potts, Los Angeles.

Branchial Cleft Cysts and Sinuses: Their Embryologic Development and Surgical Management.
William H. Re Mine, Rochester, Minn.

Cholecystectomy. R. Arnold Griswold, Louisville.

Cholecystectomy and Combined Supra and Transduodenal Exploration of the Common Duct.
Howard Mahorner, New Orleans.

Intraperitoneal Repair of Incisional Hernias with Marlex Mesh. Francis C. Usher, Houston, Texas.

Femoral Hernia with Necrotic Ileum.
Clarence Dennis, Brooklyn, and Melvin M. Newman, Denver.

Inguinal Hernioplasty.
Chester B. Mc Vay, Yankton, S. D.

Symposium on Polyps and Cancer of the Large Intestine

Moderator: Warren H. Cole, Chicago.

Participants: William Grove, John Keeley, Lester R. Dragstedt Jr., Hilger Perry Jenkins, John Van Prohaska, and Walter Maddock, Chicago, and Neil Swinton, Boston.

This series of short films will be personally narrated by the panelists as a prelude to question and answer period for audience participation. The films were produced by Dr. Jenkins.

Perforating Carcinoma. William Grove.

Polyps and Carcinoma. John Keeley.

Polyps, Diverticulitis and Carcinoma.
Lester R. Dragstedt Jr., and Hilger Perry Jenkins.

Multiple Carcinoma. John Van Prohaska.

Familial Polyposis. Walter Maddock.

Discussant. Neil Swinton.

Cold Conization of the Cervix. J. Allan Offen, Miami.

Physical Diagnosis: Communicable Diseases.
Louis Weinstein, Boston.

Physical Diagnosis: Gait and Musculo Skeletal Disorders.
William T. Green, Boston.

Resuscitation of the Newborn.
Harold Abramson, New York.

Surgical Anatomy of the Pulmonary Hilum.
Edward A. Boyden and Franklin R. Smith, Seattle.

Emergency Airway. David S. Ruhe, Kansas City, Kan.

THE SCIENTIFIC EXHIBIT

The Scientific Exhibit will be located on the main floor of the Miami Beach Exhibition Hall and Auditorium, adjacent to the Industrial Exhibits. It will open Monday, June 13, at 8:30 a. m. and will close Friday, June 17, at 12 noon. On the intervening days, the hours will be from 8:30 a. m. to 5:30 p. m.

Admission will be restricted to physicians only from 8:30 a. m. to 12 noon on Tuesday, Wednesday, and Thursday.

Each section of the Scientific Assembly has arranged a group of exhibits as in former years, dealing with its respective specialty. Emphasis is placed, however, on broad aspects of the subjects shown, rather than on specialized aspects, so that all exhibits will be of general interest.

Special features include conferences on body fluid disturbances, and pulmonary function, as well as demonstrations on fresh tissue pathology and physical examinations for physicians. Other features include exhibits on fractures, arthritis, and rheumatism, and two prize-winning exhibits selected from the Student A. M. A. Meeting as well as two from the National Science Fair.

SPECIAL FEATURES

Student American Medical Association Exhibits

The Council on Scientific Assembly has arranged for the presentation of two exhibits selected from the Annual Meeting of the Student American Medical Association in Los Angeles to be shown in the Scientific Exhibit. One exhibit will be from the resident-intern group and one exhibit from the medical student group. The exhibits are presented with the cooperation of Lakeside Laboratories, Milwaukee.

Science Fair Exhibits

The Council on Scientific Assembly has arranged for the presentation of two exhibits, selected from the National Science Fair in Indianapolis in May, to be shown in the Scientific Exhibit of the American Medical Association. The two high school students who have the best exhibits in the field of biology or medicine will accompany their exhibits and will demonstrate them during the week.

Special Exhibit on Fractures

The Special Exhibit on Fractures is presented under the auspices of the following Committee:

Ralph G. Carothers, Cincinnati, Chairman.
Harry B. Hall, Minneapolis.
Milton S. Thompson, San Antonio, Texas.

Demonstrations will be conducted simultaneously each morning and afternoon during the meeting in each of six booths on the following subjects:

Fractures About the Ankle.
Fractures of the Hip.
Fractures of the Lower End of the Radius.
Fractures of the Tibia and Fibula.
Fractures in Children.
Fractures Resulting from a Fall on the Outstretched Hand.

The demonstrations will deal with basic principles for the interest of physicians in general practice. A pamphlet dealing with the essential features of the exhibit will be distributed.

The following demonstrators will assist the Committee in the presentation of the exhibit:

Roy E. Brackin, Winnetka, Ill.
Joseph Edmund Brown, Cleveland.
Warner D. Bundens Jr., Philadelphia.
Bruce Cameron, Houston, Texas.
David M. Cameron, El Paso, Texas.
Lee J. Cordrey, Tampa, Fla.
Robert H. Denham Jr., South Bend, Ind.
John L. Doherty, Boston.
Samuel H. Fraerman, Highland Park, Ill.
Nicholas J. Giannestras, Cincinnati.
Morris E. Goldman, Lewiston, Me.
James W. Harkess, Augusta, Ga.
Kenneth T. Hubbard, Oak Park, Ill.
Richard H. Jones, Minneapolis.
William J. Kisiel, Springfield, Mass.
J. F. Kurtz, Hines, Ill.
Andrew R. Mailer, Chicago.

Problems of the Newborn—Some Questions and a Few Answers

Moderator: Warren W. Quillian, Miami

Participants: James J. Conners, Wesley S. Nock, H. Clinton Davis, and D. G. Traggis, Miami.

Friday, June 17—10 a. m.

Hyperparathyroidism and Other Disorders of Lime Salt Metabolism

Moderator: A. Gorman Hills, Miami.

Participants: John J. Farrell, Fredie Gargano, and George D. Webster Jr., Miami.

Diagnosis of Gynecologic Cancer

Moderator: J. H. Ferguson, Miami.

Participants: R. C. Forman, G. R. Gage, and Thomas F. Blake, Miami.

Certain Surgical Infections Encountered in Miami, The Gateway Between the Americas

Moderator: Joseph S. Stewart, Miami.

Participants: Frank L. Meleney, John B. Miale, and N. Joel Ehrenkranz, Miami.

MOTION PICTURE PROGRAM

MIAMI BEACH EXHIBITION HALL, ROOM B

Monday to Thursday, June 13-16

Motion pictures for the physician will be shown starting Monday afternoon and continuing daily through Thursday in Room B of the Miami Beach Exhibition Hall. The motion picture theater is located midway between the Exhibition Hall and the Auditorium. The following is a partial list of the films which will be shown on this program. Three of these films will have premiere showings at the Miami Beach Meeting.

Open Fractures. William A. Larmon, Chicago.

Coccidioidomycosis. Marco Bruschi, Bakersfield, Calif.

The Clinical Indications and Applications of Intermittent Positive Pressure Breathing.
Theodore H. Noehren, Buffalo.

Current Trends in the Clinical Management of Diabetes.
Peter H. Forsham, San Francisco, Henry Dolger, New York, and Paul Dudley White, Boston.

Symposium on the Early Detection and Medical Management of Ulcerative Colitis

Moderator: J. A. Bargen, Rochester, Minn.

Participants: Nicholas C. Hightower Jr., Temple, Texas, G. Gordon McHardy, New Orleans, Dwight Wilbur, San Francisco, and Charles H. Brown, Cleveland.

The following motion pictures will be shown as a base of the symposium and discussed:

The Early Detection and Medical Management of Ulcerative Colitis.
Nicholas C. Hightower Jr., A. Compton Broders Jr., Henry Laurens, and Richard D. Haines, Temple, Texas.

Endoscopic Diagnosis and Lower Intestinal Complications of Chronic Ulcerative Colitis.
R. J. Jackman and J. Arnold Bargen, Rochester, Minn.

Infusion Techniques of Steroids for Ulcerative Colitis.
Charles H. Brown, Cleveland.

Cerebral Vascular Disease—The Challenge of Management.
AMERICAN HEART ASSOCIATION, New York.

Rehabilitation Adds Life to Years.
AMERICAN MEDICAL ASSOCIATION, Chicago.

The Disability Decision (Premiere).
DIVISION OF DISABILITY OPERATIONS, BOASI, Baltimore, in cooperation with the AMERICAN MEDICAL ASSOCIATION.
Moderator: Raymond M. McKeown, Coos Bay, Oregon.
Participants: Arthur E. Hess, Baltimore, and George F. Gsell, Wichita.

If I Had An Ulcer. Philip Thorek, Chicago.

Closure of the Duodenal Stump in Gastric Resection.
Eurico Branco Ribeiro, Sao Paulo, Brazil.

Fecal Fistulae Following Appendectomy.
Charles Eckert, Albany.

Radical Right Colectomy—Rationale and Technique.
Robert B. Hiatt, New York.

Case of Unexplained Bleeding from the Upper Gastrointestinal Tract.
Stanley R. Friesen and Max S. Allen, Kansas City, Kansas.

Cold Knife Conization of Uterine Cervix with Dilatation and Curettage. F. J. Hofmeister, Milwaukee.

Physical Examination of the Newborn.
Mary B. Olney, San Francisco.

Management of Breast Feeding. Gordon D. Jensen, Seattle.

Cystic Fibrosis.
Henry B. Bruyn, Jackson T. Crane, and Howard Steinbach, San Francisco.

Management of Burns, Part I—Supportive Care. Part II—Local Care. Part III—Skin Grafting.
DEPARTMENT OF THE ARMY, Washington, D. C.

Chemical Tests for Intoxication (Premiere).
AMERICAN MEDICAL ASSOCIATION and AMERICAN BAR ASSOCIATION.
Remarks by: Herman A. Heise, Milwaukee, Robert F. Borkenstein, Bloomington, Indiana, and James P. Economos, Chicago.

Hypospadias: Complete Correction.
Howard B. Mays, Baltimore.

Transperitoneal Bilateral Lymphadenectomy for Testis Tumor.
WALTER REED ARMY INSTITUTE OF RESEARCH, Washington, D. C.

Undescended Testis: Surgical Anatomy of Spermatic Surgical Triangles and Lateral Spermatic Ligament.
Robert J. Prentiss, C. J. Weickgenant, J. J. Moses, and D. B. Frazier, San Diego, Calif.

Surgical Correction of Male Sterility.
V. J. O'Conor, Chicago.

Medical and Surgical Aspects of Hyperfunctioning Adrenal Cortical Lesions.
Waltman Walters, James T. Priestley, and Randall Sprague, Rochester, Minn.

Surgical Treatment of Renovascular Hypertension (Premiere).
George C. Morris Jr., E. Stanley Crawford, Denton A. Cooley, and Michael E. De Bakey, Houston, Texas.

Hospital Sepsis—A Communicable Disease.
AMERICAN MEDICAL ASSOCIATION, AMERICAN COLLEGE OF SURGEONS and AMERICAN HOSPITAL ASSOCIATION.

Skin Disinfection (Premiere). Carl Walter, Boston.

Demonstrations on Testing and Physiologic Therapy

Demonstrations will be presented each morning and afternoon to show how pulmonary function tests and physiologic therapy may be conducted in the hospital and in the office. The moderator of the session will discuss clinical applications and will receive questions or comments from the audience. The following schedule has been arranged:

Monday, June 13

10:00 a. m.
Moderator: R. Drew Miller, Rochester, Minn.
Demonstrators: Osler Abbott, Atlanta, Ga.
G. W. H. Schepers, Wilmington, Del.

2:30 p. m.
Moderator: Joseph F. Tomachefski, Columbus, Ohio.
Demonstrators: William F. Miller, Dallas, Texas.
R. H. L. Wilson, San Francisco.
Sam E. Stephenson Jr., Nashville, Tenn.

Tuesday, June 14

10:00 a. m.
Moderator: W. F. Hamilton, Augusta, Ga.
Demonstrators: James K. Alexander, Houston, Texas.
Roy F. Goddard, Albuquerque, N. Mex.
George Bower, Denver.

2:30 p. m.
Moderator: Hurley Motley, Los Angeles.
Demonstrators: Ross C. Kory, Wood, Wis.
J. W. G. Hannon, Washington, Pa.

Wednesday, June 15

10:00 a. m.
Moderator: Edwin R. Levine, Chicago.
Demonstrators: Watts Webb, Jackson, Miss.
W. Clark Cooper, Washington, D. C.

2:30 p. m.
Moderator: Albert H. Andrews Jr., Chicago.
Demonstrators: Burgess L. Gordon, Albuquerque, N. Mex.
Hylan A. Bickerman, New York.

Thursday, June 16

10:00 a. m.
Moderator: H. F. Helmholz Jr., Rochester, Minn.
Demonstrators: Joseph M. Merrill, Nashville, Tenn.
Albert Roberts, Washington, D. C.

2:30 p. m.
Moderator: Philip Samet, Miami Beach, Fla.
Demonstrators: Lloyd H. Ramsey, Nashville, Tenn.
Thomas J. Ormsby, Newark, N. J.

Friday, June 17

10:00 a. m.
Moderator: John L. Patterson Jr., Richmond, Va.
Demonstrators: Hollis G. Boren, Houston, Texas.
Robert C. Schlant, Atlanta, Ga.

Annual Physical Examinations for Physicians

"An Annual P.E. for Every M.D." will be presented by the Section on General Practice with the cooperation of the American Academy of General Practice, the American College of Cardiology, National Heart Institute, National Tuberculosis Association, National Society for the Prevention of Blindness, and Subcommittee on Noise of the Committee on Conservation of Hearing, American Academy of Ophthalmology and Otolaryngology, under the direction of the following committee:

Charles E. McArthur, Olympia, Wash., Chairman.
Meyer Sclar, Brooklyn, N. Y., Co-Chairman.
I. E. Buff, Charleston, W. Va.
Aram Glorig, Los Angeles.
John W. Ferree, New York.
Arthur M. Master, New York.
Julius L. Wilson, Philadelphia.

The local committee consists of the following:

Leon S. Eisenman, Miami, Fla.
Walter W. Sackett Jr., Miami, Fla.
M. John Hanni Jr., Miami, Fla.

Acknowledgement is made to The Burdick Corporation for electrocardiographic equipment; to the General Electric Company, X-Ray Department, for x-ray equipment featuring reduced radiation to the patient, and to the Warner-Chilcott Laboratories, Morris Plains, N. J.

The following examinations will be made:

Electrocardiograms.
Chest X-rays.
Intraocular Tension.
Audiograms.

The following consulting cardiologists will be on duty throughout the week:

Ephraim Donoso, New York.
Isadore Rosenfeld, New York.
Harry I. Russek, New York.
J. H. Silveira, Washington, D. C.
Hyman U. Solovay, Brooklyn, N. Y.
Burton Zohman, Brooklyn, N. Y.

The following are all Floridians:
Seymour Alterman.
Robert Bauer.
Jerome B. Block.
Thompson H. Boyd.
Raymond Breitbart.
Leonard Brodsky.
Joseph Burns.
Jack Cleveland.
Elliott Cohen.
David Crowell.
David Davidson.
Robert Edwards.
Ernest B. Ellis.
Clayton Fein.
Eugene Fierer.
Seymour Fine.
Eli Galitz.
Orlando Garcia.
Alvin Getz.
A. Nathan Gillman.
Joseph Glassberg.
Morton M. Halpern.
John A. Hughes.
Leonard Jacobson.
Jim S. Jewitt.
Solomon Kahn.
Bernard A. Kaminski.
Sherman Kaplan.
John M. Koval.
Maurice Krauss.
Louis Lemberg.
Milton Lesser.

Paul R. Miller, Columbus, Ohio.
William R. Moloney Jr., Los Angeles.
Glenn E. Moore, Flint, Mich.
Frank G. Murphy, Chicago.
Elwin G. Neal, Miami, Fla.
E. M. Neptune, Syracuse, N. Y.
Edward T. Newell Jr., Chattanooga, Tenn.
Theodore Norley, West Palm Beach, Fla.
Frederick G. Rosendahl, Minneapolis.
Edmund T. Rumble Jr., Callicoon, N. Y.
Lyle W. Russell, Miami, Fla.
Otto Salsbery, Covington, Ky.
James H. Spencer, Newton, N. J.
Paul Spray, Oak Ridge, Tenn.
Franklin V. Wade, Flint, Mich.
Wendell L. Whittemore, Memphis, Tenn.

Special Exhibit on Fresh Tissue Pathology

The Section on Pathology and Physiology has arranged the Special Exhibit on Fresh Tissue Pathology under the auspices of the following committee:

Philipp R. Rezek, Miami, Fla., Chairman.
W. A. D. Anderson, Coral Gables, Fla., Co-Chairman.
Samuel A. Levinson, Chicago, Section Representative.

Demonstrations will be conducted continuously on a definite schedule by a large group of competent pathologists, including guest demonstrators from teaching institutions. Guest demonstrators include outstanding pathologists from many medical schools and laboratories in the United States. Fresh pathological specimens will be supplied daily with the assistance of various hospitals and laboratories.

Jerome Benson, Miami, Fla.
Michael Bevilacqua, Miami, Fla.
Edward B. Blum, Miami, Fla.
Victor O. Calderin, Miami Beach, Fla.
Joseph H. Davis, Miami, Fla.
Robert J. Faulconer, Norfolk, Va.
C. F. Hutchison, Coral Gables, Fla.
R. A. Justi, Miami, Fla.
Charles Karpas, Miami, Fla.
Theodore C. Keller, Miami, Fla.
Dwight M. Kuhns, Harlan, Ky.
Leo Lowbeer, Tulsa, Okla.
Max Millard, Coral Gables, Fla.
Robert J. Poppiti, Fort Lauderdale, Fla.
William E. Riemer, Coral Gables, Fla.
A. M. Rywlin, Miami Beach, Fla.
Maxwell M. Sayet, Coral Gables, Fla.
T. M. Scotti, Coral Gables, Fla.
Gretchen V. Squires, Pensacola, Fla.
Ben C. Willard Jr., Orlando, Fla.
William J. Winter, Coral Gables, Fla.

Special Exhibit on Pulmonary Function

The Special Exhibit on *Pulmonary Function* is presented by the Section on Diseases of the Chest of the American Medical Association, in cooperation with the American College of Chest Physicians, the American Trudeau Society, the Industrial Medical Association, the American College of Cardiology, and the *American Association of Inhalation* Therapists, under the auspices of the following committee:

George R. Meneely, Nashville, Tenn., Chairman.
Albert H. Andrews Jr., Chicago.
Edwin R. Levine, Chicago.

Physiologic therapy as well as pulmonary *function* testing will be demonstrated. The exhibit and program of demonstrations has been developed and continued with the help of many, under the auspices of the following individuals and representatives of Government Services:

Osler Abbott, Atlanta, Ga.
Jose Alvarez Amezquita, Mexico, D. F.
Mortimer E. Bader, New York.
Richard A. Bader, New York.
Oscar J. Balchum, Los Angeles.
Alvan L. Barach, New York.
Oscar Randolph Batson, Nashville, Tenn.
Ben V. Branscomb, Birmingham, Ala.
J. J. Callaway, Nashville, Tenn.
Richard T. Cathcart, Philadelphia.
Julius Comroe Jr., San Francisco.
W. Clark Cooper, Washington, D. C.
William W. Cox, Denver.
David W. Cugell, Chicago.
David T. Dubow, Plainfield, N. J.
Jerzy Dybicki, Gdansk, Poland.
Richard V. Ebert, Little Rock, Ark.
Seymour M. Farber, San Francisco.
Oscar Feinsilver, Worcester, Mass.
Giles Filley, Denver.
Ward S. Fowler, Rochester, Minn.
Donald L. Fry, Bethesda, Md.
Edward A. Gaensler, Boston.
Burgess L. Gordon, Albuquerque, N. Mex.
Jethro Gough, Cardiff, Wales.
Ashton Graybiel, Pensacola, Fla.
W. F. Hamilton, Augusta, Ga.
J. W. G. Hannon, Washington, Pa.
H. F. Helmholz Jr., Rochester, Minn.
Joseph H. Holmes, Denver.
Nolan L. Kaltreider, Rochester, N. Y.
Ross C. Kory, Wood, Wis.
John S. LaDue, New York.
Harold A. Lyons, Brooklyn, N. Y.
Edgar Mayer, New York.
Joseph Merrill, Nashville, Tenn.
R. Drew Miller, Rochester, Minn.
Hurley L. Motley, Los Angeles.
Thomas J. Ormsby, Newark, N. J.
Frank Princi, Cincinnati.
Richard A. Prindle, Washington, D. C.
Donald F. Proctor, Baltimore.
Lloyd H. Ramsey, Nashville, Tenn.
Donald D. Reid, London.
Dickinson W. Richards, New York.
Richard Riley, Baltimore.
Albert Roberts, Washington, D. C.
A. H. Russakoff, Birmingham, Ala.
Max S. Sadove, Chicago.
John J. Sampson, San Francisco.
George A. Saxton, Chicago.
G. W. H. Schepers, Wilmington, Del.
John H. Seabury, New Orleans.
Maurice S. Segal, Boston.
Reginald H. Smart, Los Angeles.
William W. Stead, Gainesville, Fla.
Sam E. Stephenson Jr., Nashville, Tenn.
Peter A. Theodos, Philadelphia.
J. F. Tomashefski, Columbus, Ohio.
Donald S. Tysinger, Dothan, Ala.
H. S. Van Ordstrand, Cleveland.
Julius L. Wilson, Philadelphia.
Roger H. L. Wilson, San Francisco.
George Wright, Cleveland.
Attilio Omodei Zorini, Rome.

A "lung station" suitable for a hospital or clinic is designed to aid in diagnosis, prognosis, therapy, and the evaluation of disability in pulmonary disease in much the same manner that a "heart station" serves the needs of clinicians concerned with heart disease.

10:40 a. m.
Disturbances in Acid Base Balance.
Harry F. Weisberg, Chicago.

11:20 a. m.
Discussion.

Chairman: George F. Schmitt Jr., Miami, Fla.

2:00 p. m.
Nutritional Deficits: Diagnosis and Implications. Morton D. Pareira, St. Louis.

2:30 p. m.
Laboratory Aids.
Harry F. Weisberg, Chicago.

3:10 p. m.
Systematic Diagnosis: History, Symptoms, and Physical Findings.
W. D. Snively Jr., Evansville, Ind.

3:40 p. m.
Practical Assessment: Minimal Daily Program.
George F. Schmitt Jr., Miami, Fla.

4:20 p. m.
Discussion.

Thursday, June 16

Chairman: William H. Hall, Fort Sam Houston, Texas.

9:00 a. m.
Problems in Pediatric Patients.
M. J. Sweeney, Memphis, Tenn.

9:30 a. m.
Acute Renal Failure: Pathogenesis.
William H. Hall, Fort Sam Houston, Texas.

10:10 a. m.
Acute Renal Failure: Conservative Management.
William H. Hall, Fort Sam Houston, Texas.

10:40 a. m.
Acute Renal Failure: Prophylactic Hemodialysis.
Edward H. Vogel Jr., Fort Sam Houston, Texas.

11:20 a. m.
Discussion.

Chairman: James D. Hardy, Jackson, Miss.

2:00 p. m.
Routine Problems in Surgical Patients.
James D. Hardy, Jackson, Miss.

2:30 p. m.
Severe External and Internal Fluid Losses in Surgical Patients.
James D. Hardy, Jackson, Miss.

3:10 p. m.
Repair of Nutritional Deficits, Including Enteral Feedings.
Morton D. Pareira, St. Louis.

3:40 p. m.
Fluid Management in Burns.
Edward H. Vogel Jr., Fort Sam Houston, Texas.

4:20 p. m.
Discussion.

Exhibit Symposium on Arthritis and Rheumatism

The exhibit symposium on arthritis and rheumatism has been arranged by the following special committee from the American Medical Association in cooperation with the American Rheumatism Association and the Arthritis and Rheumatism Foundation:

John W. Sigler, Detroit, Chairman.
Donald F. Hill, Tucson, Ariz.
L. Maxwell Lockie, Buffalo.

A consultation booth will be available where physicians may discuss problems regarding their patients afflicted with these diseases.

Self Help Devices in Arthritis.
Edward W. Lowman, Institute of Physical Medicine and Rehabilitation of New York University-Bellevue Medical Center, New York.

Synovial Fluid Examination in Arthritis: The Simplest, Most Neglected Test for Differential Diagnosis and Effect of Therapy.
Ralph A. Jessar, Daniel J. McCarty, Ernest M. Brown Jr., and Joseph Lee Hollander, Hospital of the University of Pennsylvania, Philadelphia.

Surgical Treatment of Rheumatoid Arthritis of the Hand.
E. D. Henderson, P. R. Lipscomb, H. F. Polley, and R. H. Ferguson, Mayo Clinic and Mayo Foundation, Rochester, Minn.

Osteoarthritis: Current Concepts of Diagnosis, Management and Etiology.
David S. Howell and Roberte Slonim, University of Miami School of Medicine, Miami, Fla., and Andre Marchildon, Montreal.

The Feet in Arthritis.
John J. Calabro, Carlo Nosenzo and Felix Traugott, Seton Hall College of Medicine and Jersey City Medical Center, Jersey City, N. J.

Plaster Casts and Splints in the Care of Patients with Rheumatoid Arthritis.
David M. Fried, Joseph J. Bunim and Mario L. Salvanelli, National Institutes of Health, Bethesda, Md.

Do You Have a Question, Doctor?
Donald F. Hill, Tucson, Ariz., L. Maxwell Lockie, Buffalo, and John W. Sigler, Detroit.

Serological Reactions in the Connective Tissue Diseases.
Arthur P. Hall, Theodore B. Bayles, and Wadi A. Bardawil, Robert B. Brigham Hospital, Boston.

Information on Arthritis.
Ronald W. Lamont-Havers, The Arthritis and Rheumatism Foundation, New York.

Gout: Its Diagnosis and Treatment.
Thomas E. Weiss, Albert Segaloff and William H. Schindel, Ochsner Clinic, New Orleans.

Differential Diagnosis of Shoulder Pain.
Joseph L. Fleming, Robert S. Knighton, John W. Sigler, and William C. Noshay, Henry Ford Hospital, Detroit.

Surgery of the Arthritic Hand.
Rolla D. Campbell Jr., Robert C. Mellors, John L. Sbarbaro, and L. Ramsay Straub, Hospital for Special Surgery, New York.

The Patient with Rheumatic Disease: What is Your Diagnosis?
Kenneth M. Kron, Irvin F. Hermann, Richard T. Smith, and John C. Richards, Benjamin Franklin Clinic, Pennsylvania Hospital, Philadelphia.

Gerardo H. Martinez.
David A. Nathan.
Kenneth Phillips.
William C. Phillips.
Edwin P. Preston.
George Pullias.
Harry B. Rimer.
Hunter Rogers.
Philip Samet.
M. Murray Schechter.
Sylvan A. Schotz.
C. Leon Shalloway.
Charles W. Silverblatt.
William Smith.
Leonard Sommer.
Donald Stannus.
Edward St. Mary.
William Straight.
Earl Templeton.
Walter Tobin.
Rudolph Wagner.
Charles Wigderson.
Elliott Witkind.
Scheffel Wright.
Maurice Zimmerman.
Paul Zimmerman.
Nelson Zivitz.

Special Exhibit and Clinical Forum on Body Fluid Disturbances

The Special Exhibit and Clinical Form on Body Fluid Disturbances is presented under the auspices of the following committee:

William D. Snively Jr., Evansville, Ind., Chairman.
William A. Hall, Fort Sam Houston, Texas.
James D. Hardy, Jackson, Miss.
Morton D. Pareira, St. Louis.
George F. Schmitt Jr., Miami, Fla.
M. J. Sweeney, Memphis, Tenn.
Edward H. Vogel Jr., Fort Sam Houston, Texas.
Harry F. Weisberg, Chicago.

Exhibits will be demonstrated by some of the speakers to supplement their presentations. The program follows:

Monday, June 13

Chairman: Harry F. Weisberg, Chicago

9:00 a. m.
Foundation Facts: Anatomic, Physiologic and Chemical—Part I.
W. D. Snively Jr., Evansville, Ind.

9:30 a. m.
Foundation Facts: Anatomic, Physiologic and Chemical—Part II.
George F. Schmitt Jr., Miami, Fla.

10:10 a. m.
Diagnostic Images of Disturbances in Volume, Concentration, Composition and Position of Body Fluids.
M. J. Sweeney, Memphis, Tenn.

10:40 a. m.
Disturbances in Acid Base Balance.
Harry F. Weisberg, Chicago.

11:20 a. m.
Discussion.

Chairman: W. D. Snively Jr., Evansville, Ind.

2:00 p. m.
Nutritional Deficits: Diagnosis and Implications.
Morton D. Pareira, St. Louis.

2:30 p. m.
Laboratory Aids.
Harry F. Weisberg, Chicago.

3:10 p. m.
Systematic Diagnosis: History, Symptoms, and Physical Findings.
W. D. Snively Jr., Evansville, Ind.

3:40 p. m.
Practical Assessment: Minimal Daily Program.
George F. Schmitt Jr., Miami, Fla.

4:20 p. m.
Discussion.

Tuesday, June 14

Chairman: Edward H. Vogel Jr., Fort Sam Houston, Texas.

9:00 a. m.
Problems in Pediatric Patients.
M. J. Sweeney, Memphis, Tenn.

9:30 a. m.
Acute Renal Failure: Pathogenesis.
William H. Hall, Fort Sam Houston, Texas.

10:10 a. m.
Acute Renal Failure: Conservative Management.
William H. Hall, Fort Sam Houston, Texas.

10:40 a. m.
Acute Renal Failure: Prophylactic Hemodialysis.
Edward H. Vogel Jr., Fort Sam Houston, Texas.

11:20 a. m.
Discussion.

Chairman: Morton D. Pareira, St. Louis

2:00 p. m.
Routine Problems in Surgical Patients.
James D. Hardy, Jackson, Miss.

2:30 p. m.
Severe External and Internal Fluid Losses in Surgical Patients.
James D. Hardy, Jackson, Miss.

3:10 p. m.
Repair of Nutritional Deficits, Including Enteral Feedings.
Morton D. Pareira, St. Louis.

3:40 p. m.
Fluid Management in Burns.
Edward H. Vogel Jr., Fort Sam Houston, Texas.

4:20 p. m.
Discussion.

Wednesday, June 15

Chairman: M. J. Sweeney, Memphis, Tenn.

9:00 a. m.
Foundation Facts: Anatomic, Physiologic, and Chemical—Part I.
W. D. Snively Jr., Evansville, Ind.

9:30 a. m.
Foundation Facts: Anatomic, Physiologic, and Chemical—Part II.
George F. Schmitt Jr., Miami, Fla.

10:10 a. m.
Diagnostic Images of Disturbances in Volume, Concentration, Composition, and Position of Body Fluids.
M. J. Sweeney, Memphis, Tenn.

Selective Coronary Arteriography: An Improved Method for Evaluating Patients with Coronary Heart Disease.
M. S. Mazel, Fernando Tapia, and Houck Bolton, Edgewater Hospital, Chicago.

Aortic and Pulmonic Stenosis: Diagnosis and Surgical Treatment.
Conrad R. Lam, Rodman E. Taber, Edward Green, Ellet Drake, Henry Ford Hospital, Detroit.

A Practical Test of Ventilatory Function.
Jack D. Hackney, Clarence R. Collier, Carl Bauer, and Donald E. Griggs, College of Medical Evangelists and Los Angeles County Hospital, Los Angeles.

Digitalis Sensitivity in Chronic Pulmonary Insufficiency.
Morris M. Dick, George L. Baum and Charles W. Silverblatt, Veterans Administration Hospital and University of Miami School of Medicine, Coral Gables, Fla.

The Precordial Electrocardiogram During Exercise.
Alvin H. Freidman, Ramon Abarquez, Fredric Reichel, and John S. LaDue, Memorial Center for Cancer and Allied Diseases, New York.

Surgical Approach to Pulmonary Emphysema.
Otto C. Brantigan, Milton B. Kress, and Eugene A. Mueller, Church Home and Hospital, Baltimore.

Rapid Sensitivity Medium for Tuberculosis.
Jack Reiss and Sam M. Townsend, Veterans Administration Hospital, Coral Gables, Fla.

Cardiac Arrest and Resuscitation: Actual Practice in Cardiac Massage.
W. R. Rumel, Rumel Chest Clinic and Latter-day Saints Hospital, Salt Lake City.

Your Risk of Lung Cancer.
Lewis C. Robbins, Cancer Control Program, Public Health Service, Washington, D. C.

Section on Experimental Medicine and Therapeutics

The representative to the Scientific Exhibit from the Section on Experimental Medicine and Therapeutics is Joseph F. Ross, Los Angeles.

Experimental and Clinical Use of Fibrinolysin.
Paul W. Boyles and Jack Graff, Miami Heart Institute, Miami Beach, Fla.

Pathology and Physiology of the Thoracic Duct Lymph.
Alvin L. Watne, Imran Hatiboglu, and George E. Moore, Roswell Park Memorial Institute, Buffalo.

Twenty Years' Experience with Oral Anticoagulant Therapy.
Shepard Shapiro, New York.

Clinical Evaluation of New Drugs.
K. G. Kohlstaedt, S. O. Waife and J. M. Maas, Lilly Research Laboratories, Indianapolis.

Clinical-Pharmacological Studies with Chymotrypsin.
Albert J. Levine, Charles Beck, Oscar F. Davis, Bernard Horwitz, Chicago Medical School, and Stritch School of Medicine of Loyola University, Chicago.

The Effect of Serotonin and Histamine on Vascular Reactivity and Connective Tissue.
Arthur L. Scherbel, John W. Harrison and Victor G. deWolfe, The Cleveland Clinic Foundation, Cleveland.

Treatment of Thrombo-embolic Disease with Human Fibrinolysis: Methods of Activation and Action.
Eugene E. Cliffton and Carlo Grossi, Cornell University Medical College and Sloan-Kettering Institute for Cancer Research, New York.

Radiodiagnostic Tests in Liver and Kidney Diseases.
George V. Taplin and Delores E. Johnson, University of California School of Medicine and Harbor General Hospital, Los Angeles.

Fetal Electrocardiography.
Saul David Larks, University of California School of Medicine, Los Angeles.

New Chemotherapy of Systemic Mycoses: Experiment and Clinical Studies.
Chester W. Emmons and John P. Utz, National Institutes of Health, Bethesda, Md.

Pharmacodynamics of Primary Hypertension.
Benjamin Calesnick and Joseph R. DiPalma, Hahnemann Medical College, Philadelphia.

Mechanical Assistance in Experimental Heart Failure and Cardiogenic Shock.
Peter F. Salisbury, St. Joseph Hospital, Burbank, Calif.

Tranquilizers in Medical Practice: Use and Abuse.
J. H. Nodine, T. Bodi, P. Siegler, J. Slap, and J. H. Moyer, Hahnemann Medical College and Hospital, Philadelphia.

Measuring Physical States and Effects of Medications by the Use of a Performance Indicator.
Leo J. Cass and Willem S. Frederik, University Health Services, Harvard University, Cambridge, Mass.

The Circulatory Effects of a Stressor System.
Alfred Halpern, Paul Kuhn, David Selman, and Norman Shaftel, American College of Angiology, Great Neck, N. Y.

The Practical Management of the Agitated Alcoholic.
Leon J. Weiner and Albert A. Bockman, Philadelphia General Hospital, Philadelphia.

The Role of Endogenous Humoral Agents in Migraine.
Adrian M. Ostfeld, University of Illinois College of Medicine, Chicago.

Chemotherapeutic Control of Cancer.
Jeanne C. Bateman and Harry N. Carlton, Washington, D. C.

Automatic Measurement of Blood Glucose and Oral Hypoglycemic Agents.
Charles Weller, Morton Linder, Alice Macaulay, Andres Ferrari, and Gerald Kessler, Grasslands Hospital, Valhalla, N. Y.

Fibrinolysin in Clinical Therapy.
R. V. Chapple, T. R. C. Sisson and H. O. Singher, Ortho Research Foundation, Raritan, N. J.

Reduction of Serum Lipids and other Metabolic Effects of Nicotinic Acid.
William B. Parsons Jr., Jackson Clinic and Foundation, Jackson, Wis.

Supplemental Uses of a Parallel Flow Dialyzer.
Sidney Anthone, Richard W. Egan, Roland Anthone, Arthur E. MacNeill, Jose A. Rodriguez, University of Buffalo School of Medicine and Buffalo General Hospital, Buffalo.

SECTION EXHIBITS

Each of the 21 sections of the Scientific Assembly has arranged a group of exhibits dealing with the various branches of medicine.

Section on Anesthesiology

The representative to the Scientific Exhibit from the Section on Anesthesiology is Edwin L. Rushia, Augusta, Ga.

Why Blood Volume in Surgery?
Reuben C. Balagot, William Grove, Eugene Jorgen, and Max S. Sadove, University of Illinois College of Medicine, Chicago.

The Prevention of Serious Airway Complications During Anesthesia.
Frank E. Fierro, Dante Bizzarri, Albert Schmookler, Francis S. Latteri, Joseph Giuffrida, and Howard C. Berger, New York Medical College—Metropolitan Medical Center, New York.

Drug Action Measured by Rotating Explants of Human Respiratory Epithelium.
Gunter Corssen, C. George Lefeber, Earl E. Pitsinger, and Charles R. Allen, University of Texas Medical Branch, Galveston, Texas.

Regulation of Body Temperature in Infants and Children.
C. R. Stephen and Robert D. MacMillan, Duke University Medical Center, Durham, N. C.

The Significant Effects of Hypotension and Hypertension in Anesthesia.
D. E. Hale and L. J. McCormack, Cleveland Clinic, Cleveland.

Fallacies and Misconceptions Concerning Anesthesia for Infants and Children.
John Adriani, George Sessions, and Thomas Upton, Louisiana State University School of Medicine and Charity Hospital, New Orleans.

Regional Hypothermia and Its Effect on the Brain.
H. B. Benjamin, Marvin Wagner, H. K. Ihrig, Walter Zeit, G. E. Bartenbach, and A. B. Becker, Marquette University, School of Medicine, Milwaukee.

Clinical Applications of Ganglionic Blockade.
Antonio Boba, Albany Medical College of Union University, Albany, N. Y.

Section on Dermatology

The representative to the Scientific Exhibit from the Section on Dermatology is Stanley E. Huff, Evanston, Ill.

Management of Pyoderma.
Samuel M. Bluefarb, Northwestern University Medical School and Cook County Hospital, Chicago.

Therapy of Skin Infections Commonly Seen in General Practice.
William C. Miller, Wausau, Wis.

Diagnosis of Xanthomatosis.
Paul R. Winder, Richard M. Caplan, Walter D. Block, and Arthur C. Curtis, University of Michigan Hospital, Ann Arbor, Mich.

The Pathologic Dynamics of Acne Vulgaris.
John S. Strauss, Boston University School of Medicine, Boston, and Albert M. Kligman, University of Pennsylvania School of Medicine, Philadelphia.

The Recognition of Hansen's Disease.
Arlington Bensel, Orange, N. J.

Inside X-ray.
Paul M. Crossland, Stanford University School of Medicine, Palo Alto, Calif.

The Control of Staphylococcal Infection on a Dermatology Service of a General Hospital.
William Cohen and Ruth M. Hotz, Cincinnati General Hospital, Cincinnati.

Acne: Should We Limit Sugar?
Theodore Cornbleet, Irma Gigli, and J. J. Jambor, University of Illinois College of Medicine, Chicago.

Bowen's Disease and Its Relationship to Systemic Cancer.
James H. Graham and Elson B. Helwig, Armed Forces Institute of Pathology, Washington, D. C.

Griseofulvin in the Treatment of Fungus Infections.
J. Walter Wilson, John W. Carney and Alfred W. Graves, University of Southern California School of Medicine, Los Angeles.

Tricophyton Verrucosum Infections of the Skin.
James M. Flood, Guthrie Clinic, Sayre, Pa.

Dexamethasone by Mouth in Chronic Dermatoses.
John F. Daly, University of Vermont College of Medicine, Burlington, Vt.

Section on Diseases of the Chest

The representative to the Scientific Exhibit from the Section on Diseases of the Chest is Edwin Rayner Levine, Chicago. The Section is also sponsoring the Special Exhibit on Pulmonary Function.

Mediastinal Tumors.
W. L. Watson, John L. Pool, W. G. Cahan, R. J. Luomanen, E. E. Cliffton, and J. T. Goodner, Memorial Center for Cancer and Allied Diseases, New York.

The Solitary Pulmonary Nodule.
Walton M. Edwards, 2nd General Hospital, New York.

Circulatory Changes of Vital Organs During Cardiac Arrhythmias.
Eliot Corday, David Irving and Herbert Gold, Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles.

The Measurement of Blood Flow Through Extracorporeal Circuits.
Paul W. Sanger, Francis Robicsek and Frederick H. Taylor, Charlotte Memorial Hospital, Charlotte, N. C.

Subgross Pulmonary Anatomy in Various Mammals and Man.
Richard F. McLaughlin Jr., Walter S. Tyler, Robert O. Canada, and Gerald L. Crenshaw, U. S. Naval Hospital, Oakland, Calif., and University of California School of Veterinary Medicine, Davis, Calif.

Pericardial Diseases: Their Recognition and Management.
D. C. Connolly, O. T. Clagett, J. E. Edwards, H. B. Burchell, and A. H. Bulbulian, Mayo Clinic and Mayo Foundation, Rochester, Minn.

Steroids Activate Tuberculosis.
Julius L. Wilson and Floyd M. Feldmann, American Trudeau Society and National Tuberculosis Association, New York.

Observed and Anticipated Advantages of a New Concept of Baby Feeding and Raising.
Walter W. Sackett Jr., and Mary M. Sackett, Doctor's Hospital, Coral Gables, Fla.

Emotional Disorders in General Practice.
Blaine E. McLaughlin, Woman's Medical College of Pennsylvania, Philadelphia.

Mechanisms Involved in Weight Reduction.
Peter H. Forsham, Burt Cochran Jr., and Charles Watlington, University of California School of Medicine, San Francisco.

Severe Agitation: Treatment with Methaminodiazepoxide, A New Psychosedative.
John D. Schultz, District of Columbia General Hospital, Washington, D. C.

Methandrostenolone, An Anabolic Agent.
Robert B. Greenblatt, Edwin C. Jungck, and William E. Barfield, Medical College of Georgia, Augusta, Ga.

Section on Internal Medicine

The representative to the Scientific Exhibit from the Section on Internal Medicine is Henry T. Ricketts, Chicago.

Anti-inflammatory Adrenocorticoids.
Thomas H. McGavack, Hans G. Bauer, and Kung-Ying Tang Kao, Veterans Administration Center, Martinsburg, W. Va.

Use of Radioisotopes to Record Myocardial Blood Flow Changes Produced by Coronary Dilators.
Philip C. Johnson and Gunnar Sevelius, University of Oklahoma Medical Center, Oklahoma City, Okla.

Simple Effective Weight Reduction.
I. Frank Tullis, Charles E. Allen, and Richard R. Overman, University of Tennessee College of Medicine, Memphis.

Tissue Vulnerability, Inflammation and the Nervous System.
Loring F. Chapman, Helen Goodell, and Harold G. Wolff, Cornell University Medical College and New York Hospital, New York.

Salicylate Therapy in Rheumatoid Arthritis.
R. E. Heering and R. H. Jacques, Ohio State University College of Medicine, Columbus, Ohio.

Strokes.
Vergil N. Slee, G. Stanley Woodson, and Lorenzo Rodriguez-Peralta, Commission on Professional and Hospital Activities, Ann Arbor, Mich.

Everyday Problems in Diabetes. 201 Crystal-Clear Answers.
Francis D. W. Lukens and Mark I. Hewitt, American Diabetes Association, Inc., New York.

Long Term Corticosteroid Therapy in Bronchial Asthma.
Emanuel Schwartz, Long Island College Hospital–State University of New York Downstate Medical Center, New York City.

Curable Hypertension.
Shannon Brunjes, Varner J. Johns Jr., and Milton G. Crane, College of Medical Evangelists, Los Angeles.

Hereditary Hyperparathyroidism.
Charles E. Jackson, Pierre C. Talbert, and Harold D. Caylor, Caylor-Nichel Clinic, Bluffton, Ind.

Premenstrual Tension with Cyclic Weight Gain.
Alice I. Macaulay, Grasslands Hospital, Valhalla, N. Y., and Marvin Moser, White Plains, N. Y.

The Value of the Scintigram in the Diagnosis of Thyroid Disease.
J. Martin Miller, Melvin A. Block and Raymond Mellinger, Henry Ford Hospital, Detroit.

Influence of a Hot and Humid Environment on the Cardiovascular System of Man.
George E. Burch and Nicholas DePasquale, Tulane University of Louisiana School of Medicine, New Orleans.

Progressive Renal Injury and Disease in Orthostatic Proteinuria.
S. Edward King, New York City Department of Health, New York.

A Simplified Method of Diagnosing, Differentiating and Treating Diabetic Acidosis and Insulin Shock.
R. A. MacHaffie, Veterans Administration Hospital, Roseburg, Ore.

Long-Term Anticoagulants for Coronary Atherosclerosis.
E. Sterling Nichol, William C. Phillips, and Gus G. Casten, Miami Heart Institute, Miami Beach, Fla.

Hypertension Crises: Diagnosis and Treatment.
William K. Jensen, Garfield G. Duncan, Robert J. Gill, Richard B. Freeman, and William T. Brandfass, The Pennsylvania Hospital, Philadelphia.

Obesity and the Circulation.
J. K. Alexander, E. W. Dennis, R. Sakaguchi, K. H. Amad, and V. W. Cole, Baylor University College of Medicine, Houston, Texas.

Is Physical Diagnosis a Lost Art?
Maxwell L. Gelfand, Theodore Cohen and Louis Goodkin, New York University-Postgraduate Medical School and New York University Bellevue Medical Center, New York.

Simulated Constant Mass Ballistocardiography by Periodic and Aperiodic Systems.
Jan Nyboer, Harper Hospital, David Jay, Ford Motor Company, and Robert Davidson, Wayne State University College of Medicine, Detroit.

Visceral Aneurysms: Importance of Recognition and Treatment of These Potentially Serious Lesions.
J. F. Fairbairn II, J. A. Spittel Jr., P. J. Osmundson, G. D. David, and O. W. Kincaid, Mayo Clinic and Mayo Foundation, Rochester, Minn.

Osteoporosis.
Harry E. Banghart, Germantown Dispensary and Hospital, Philadelphia.

Section on Laryngology, Otology and Rhinology

The representative to the Scientific Exhibit from the Section on Laryngology, Otology and Rhinology is Walter H. Maloney, Cleveland.

Fenestration of the Oval Window.
John J. Shea, Memphis Otologic Clinic, Memphis, Tenn.

Peritoneal Dialysis: Technique and Applications.
MORTON H. MAXWELL, ROBERT E. ROCKNEY, and CHARLES R. KLEEMAN, University of California School of Medicine, Los Angeles.

The Respiratory Analeptic, Vanillic Diethylamide, in Severe Respiratory Failure.
WILLIAM F. MILLER, RICHARD K. ARCHER, and HAROLD F. TAYLOR, University of Texas, Southwestern Medical School, and Parkland Memorial Hospital, Dallas, Texas.

Section on Gastroenterology and Proctology

The representatives to the Scientific Exhibit from the Section on Gastroenterology and Proctology are GEORGE GORDON McHARDY, New Orleans, and THOMAS E. MACHELLA, Philadelphia.

Pathophysiology, Diagnosis, and Treatment of Ulcerative Colitis.
J. ALFRED RIDER, HUGO C. MOELLER, RICHARD G. DEVEREAUX, ERNESTO J. PULETTI LOURDES F. ACCAOILI, JOEL FYVOLENT, MICHAEL GEOKAS, JOHN O. GIBBS, and JOYCE SWADER, University of California Medical Center, San Francisco.

Diagnosis and Treatment of Functional Diarrhea.
DONALD BERKOWITZ and MARVIN ROTMAN, Albert Einstein and Sidney Hillman Medical Centers, and Hahnemann Medical College, Philadelphia.

Peptic Ulcer, Ulcer Diets and Coronary Heart Disease.
DAVID J. SANDWEISS, MARCUS H. SUGARMAN, RICHARD REMINGTON, GILBERT M. BERMAN, JACK A. LITWIN, MARION E. MANN, and ALICE BEECHER, Sinai and Harper Hospitals of Detroit, and School of Public Health, Ann Arbor, Mich.

Duodenal Ulcer: Current Concepts.
GORDON McHARDY, ROBERT J. McHARDY, HELEN VAN FOSSON, and SWAN S. WARD, Louisiana State University School of Medicine, New Orleans.

Polyps and Cancer.
RICHARD B. CATTELL, NEIL W. SWINTON and WILLIAM MEISSNER, Lahey Clinic, Boston.

Proctoscopic Manikins: Teaching the Art of Proctoscopy.
FREDERICK STENN, DURAND SMITH, and MICHAEL GOVOSTIS, Northwestern University Medical School, KHALID DURRANI, Englewood Hospital, MILAN WASICK, University of Illinois College of Medicine, and JOSEPH LEVENSON, Chicago Medical School, Chicago.

Diverticulitis and Diverticulosis of the Large Bowel.
PAUL T. CARROLL, Columbus, Ohio.

Section on General Practice

The representative to the Scientific Exhibit from the Section on General Practice is I. PHILLIPS FROHMAN, Washington, D. C. The Section is conducting physical examinations for physicians.

The Diagnosis and Treatment of Cervical Disc Disease.
GEORGE W. SMITH and FRANCES DEROLLER, Medical College of Georgia, Augusta, Ga.

The Management of Shock.
ARTHUR BERNSTEIN, FRANKLIN SIMON, JEROME KAUFMAN, FRED B. COHEN, BERNARD ROBINS, and EDWIN L. ROTHFELD, Newark Beth Israel Hospital, Newark, N. J.

The Practical Management of Chest Injuries.
ROBERT G. TROUT, JULIO C. DAVILA, and ROBERT P. GLOVER, Presbyterian and Fitzgerald Mercy Hospitals, Philadelphia.

Glaucoma—The Physicians Role in Early Detection.
CONRAD BERENS, PATRICIA RAINIER, and ALFONSE CINOTTI, The Ophthalmological Foundation, Inc., New York.

Pelvic Inflammatory Disease: Chymotrypsin Therapy.
WALTER J. REICH and MITCHELL J. NECHTOW, Cook County Hospital, Chicago Medical School and Cook County Postgraduate School of Medicine, Chicago.

Legal Snares for the Physician.
HAROLD LEFKOE, American Board of Legal Medicine, Philadelphia.

Monoamine Oxidase Inhibitors in Angina Pectoris.
HENRY I. RUSSEK, U. S. Public Health Service Hospital, New York.

Newer Approaches to Management of Lethargic States.
RAYMOND J. GADEK and HAROLD S. FELDMAN, Perth Amboy, N. J.

Cytology in General Practice.
HERMAN E. HILLEBOE, New York State Department of Health, Albany, N. Y.

Types of Clinical Investigation by the General Physician in His Practice.
I. PHILLIPS FROHMAN, Washington, D. C.

Hypothermia in Clinical Medicine.
R. ADAMS COWLEY, EMIL BLAIR, PAUL HACKETT, JOHN ALLEN, and JAMES ESTES, University of Maryland School of Medicine, Baltimore.

The Lost Art of Urinalysis.
VICTOR E. POLLAK, ROBERT M. KARK, ROBERT C. MUEHRCKE, and CONRAD L. PIRANI, University of Illinois College of Medicine, Chicago.

Migrant Worker Exhibit.
WILLIAM G. YANNIELLO and HELEN L. JOHNSTON, Public Health Service, U. S. Department of Health, Education, and Welfare, Washington, D. C.

Strike Back at Arthritis.
JOSEPH J. BUNIM, BERNARD D. DAITZ, WILFRED D. DAVID, and DAVID M. FRIED, U. S. Public Health Service, Washington, D. C., and RONALD W. LAMONT-HAVERS, The Arthritis and Rheumatism Foundation, New York.

Management of the Obese Diabetic.
S. K. FINEBERG, Harlem Hospital, New York.

Oral Hypoglycemic Agents in the Treatment of Diabetes Mellitus.
JAMES M. MOSS, DEWITT E. DELAWTER, and SIDNEY A. TYROLER, Georgetown University Medical Center, Washington, D. C.

The Prevention and Correction of Deformity by Splints.
NORRIE SWANSON, Toronto General Hospital and Sunnybrook Veterans Hospital, Toronto.

Adenomas and Cancer of the Colon and Rectum.
ROBERT TURELL, The Mount Sinai Hospital, New York. York.

If I Had an Ulcer.
PHILIP THOREK, Chicago.

Carcinoma of the Cervix: A Curable Disease, A Preventable Disease.
Ervin E. Nichols and A. Warren Olson, College of Medical Evangelists, Los Angeles.

Pathogenesis and Therapy of Premenstrual Tension.
Alvin F. Goldfarb, Jefferson Medical College, Philadelphia.

Cervical Cytology—A Gynecologic Challenge.
J. Allan Offen and James Henry Ferguson, University of Miami School of Medicine, Miami, Fla.

Enzymatic Control of Untoward Effects in Conization of the Cervix.
Lowell F. Bushnell, Camarillo State Hospital, Camarillo, Calif.

Control of Arteriole Bleeding in Obstetrics.
William Fitzgerald, A. N. Brady Maternity Hospital, Albany Medical College, Albany, N. Y.

Maternal and Fetal Effects of Obstetric Analgesia.
John C. Ullery and C. Ray Potts, Ohio State University College of Medicine, Columbus, Ohio.

The Fateful Months when Life Begins.
Richard L. Masland, National Institutes of Health, Bethesda, Md.

The Use of Synthetic Oxytocin.
Robert H. Stewart, Roy M. Slezak, and Robert N. Nelson, University of Washington School of Medicine and The Swedish Hospital, Seattle.

Effective Control of "Toxemia."
Herbert E. Schmitz, Michael P. MacLaverty, and Robert S. Pavlic, Stritch School of Medicine of Loyola University, Chicago.

Prevention and Management of Prematurity.
Frederick H. Falls and Charlotte S. Holt, Illinois State Department of Public Health, Springfield, Ill.

Treatment of Biliary Stasis in Latter Half of Pregnancy.
C. George Muscillo and Stephen W. Giorlando, Fordham Hospital, Bronx, N. Y.

Control of Emesis Gravidarum: Private Practice Clinical Study.
Robert D. Dunn, Palo Alto Clinic, Palo Alto, Calif., and Leon P. Fox, Santa Clara County Hospital, San Jose, Calif.

Section on Ophthalmology

The representative to the Scientific Exhibit from the Section on Ophthalmology is Franklin W. Newell, Chicago.

Anterior Chamber Lenses.
DuPont Guerry III, Walter J. Geeraets, and Wolfgang A. Lieb, Medical College of Virginia and Titmus Research Laboratory, Richmond, Va.

Retinal Tears in Autopsy Eyes.
Edward Okun, Washington University School of Medicine, St. Louis.

Chamber Angle Anomalies in Developmental Glaucoma and in Systemic Mesodermal Disorders.
Hermann M. Burian, Gunter K. von Noorden, Lee Allen, and Ignacio V. Ponseti, University Hospitals and State University of Iowa College of Medicine, Iowa City.

Clinical—Pathological Correlation of Selected Eye Diseases.
Victor T. Curtin and Edward W. D. Norton, University of Miami School of Medicine, Miami, Fla.

Ophthalmodynomometry: A Diagnostic Aid in Cerebrovascular Disease.
Robert A. Schimek and Homer D. Kirgis, Ochsner Clinic and Tulane University of Louisiana School of Medicine, New Orleans.

Clinical Use of Urea for the Reduction of Intraòcular Pressure.
M. J. Javid and M. D. Davis, University Hospitals, Madison, Wis.

Use of Light Coagulator in Retinal Detachment.
William H. Havener and Torrence A. Makley, Ohio State University College of Medicine, Columbus, Ohio.

Pathology of Ocular Leprosy.
James H. Allen and Jerome L. Byers, Tulane University of Louisiana School of Medicine, New Orleans.

Congenital Anomalies of the Eye.
Everet H. Wood, Lovelace Clinic and Lovelace Foundation, Albuquerque, N. Mex.

Clinicopathologic Study of the Cornea.
Lorenz E. Zimmerman, Armed Forces Institute of Pathology, Washington, D. C., William F. Hughes, University of Illinois College of Medicine, Chicago, and Sam T. Jones, University of Oregon Medical School, Portland, Ore.

Section on Orthopedic Surgery

The representative to the Scientific Exhibit from the Section on Orthopedic Surgery is James I. Kendrick, Cleveland.

Skeletal Anomalies Associated with Myelomeningocele, Diastematonyelia and Syringomyelia.
W. James Gardner and John S. Collis, Cleveland Clinic, Cleveland.

Congenital Plantar Flexed Talus.
Frederick S. Craig, New York Orthopaedic Hospital in The Columbia Presbyterian Medical Center, New York.

Eosinophilic Granuloma of Bone.
Kenneth C. Francis, Henry Selby, and John L. Sbarbaro Jr., Bone Service, Memorial Center for Cancer and Allied Diseases, and The Hospital for Special Surgery, New York.

Posterolateral Fusion of the Lumbosacral Spine.
George Truchly, New York Veterans Administration Hospital, and Walter A. L. Thompson, New York University Bellevue Medical Center, New York.

Hoke Method of Treatment of Femoral Shaft Fractures in Children.
John R. Moore, Arthur F. Seifer, John W. Lachman, and Howard H. Steel, Temple University Medical Center, Philadelphia.

Direct Magnification Radiography in Orthopedics.
I. E. Fixel, Hollywood, Fla.

Common Soft Tissue Tumors of the Hand.
Forrest H. Foreman, Arturo Ortiz, and Creighton L. Wilson, University of Miami School of Medicine, Miami, Fla.

Caloric Test Studies of the Neurolabyrinthine Mechanism.
David A. Dolowitz, University of Utah School of Medicine, Memorial Medical Center, Salt Lake City.

The Pathogenesis of Acute External Otitis.
Edley H. Jones and Tom D. Norman, University of Mississippi School of Medicine, Jackson, Miss.

The Mechanics of the Crico-Arytenoid Joint.
Hans Von Leden and Paul Moore, Northwestern University Medical School—The William and Harriet Gould Foundation, Chicago.

Cancer of the Larynx.
Edward C. Brandow Jr., Albany Hospital—Albany Medical College, Albany, N. Y.

Use of Plastics in Ear Surgery.
James L. Sheehy, Howard P. House, William F. House, and Fred H. Linthicum Jr., University of Southern California School of Medicine, Los Angeles.

Oncology of Head and Neck: Primary and Reconstructive Surgery.
Richard T. Farrior and Garland Dummit, Tampa, Fla.

The Maxilla-Premaxilla Approach to Extensive Nasal Septum Surgery.
Maurice H. Cottle, Ralph H. Riggs, Roland M. Loring, and Irwin E. Gaynon, Chicago Medical School, Chicago.

Otologic Microsurgery: Otosclerosis Surgery and Tympanoplasty.
David Myers, Woodrow D. Schlosser, Arnold K. Brenman, Lindsay L. Pratt, and Richard A. Winchester, Temple University Medical Center, Philadelphia.

Section on Military Medicine

The representative to the Scientific Exhibit from the Section on Military Medicine is Frank M. Townsend, Washington, D. C.

American Registry of Pathology, Armed Forces Institute of Pathology.
Frank M. Townsend, Joe M. Blumberg, and T. R. Austin, Armed Forces Institute of Pathology, Washington, D. C.

Rapid Hypothermia: A New Extracorporeal Method.
Harold C. Urschel and Jack J. Greenberg, Medical Research Institute, Bethesda, Md.

Aerospace Physiology.
Smith W. Ames and Lawrence W. Weber, Armed Forces Institute of Pathology, Washington, D. C.

Macropathology: An Ancient Art—a New Science.
Frank M. Townsend, Roger H. Fuller, and Albert E. Minns Jr., Armed Forces Institute of Pathology, Washington, D. C.

Leptospirosis in the Americas.
Gordon W. Vacura, Walter Reed Army Institute of Research, Washington, D. C.

Aerospace Crew Effectiveness.
Charles Berry, Armed Forces Institute of Pathology, Washington, D. C.

Splenoportography.
B. H. Sullivan, Robert D. Gamble, and Longstreet C. Hamilton, Walter Reed Army Hospital, Washington, D. C.

Management of Severe Burns by Modified Exposure.
Edward H. Vogel Jr., Wilfred T. Tumbusch, a
Duane L. Larson, United States Army Surgic
Unit, Brooke Army Medical Center, Fort Sam Hou
ton, Texas.

Angiography: A Surgical Adjunct.
William F. Hughes, Charles E. Rogers, and Nicol
A. Garcia III, United States Naval Hospital,
Albans, L. I., N. Y.

Section on Nervous and Mental Diseases

The representative to the Scientific Exhibit from the Se
tion on Nervous and Mental Diseases is Benjamin Bosh
Chicago.

**Cerebrovascular Disease: Approach to Diagnosis and Ma
agement.**
E. S. Gurdjian, W. G. Hardy, D. W. Lindner,
Croll, S. J. Figiel, J. E. Lofstrom, J. E. Webst
and J. L. Whelan, Wayne State University Coll
of Medicine, Detroit.

**The Treatment of Radiculopathy with Epidural Hydroc
tisone.**
Stanley Jallo, William Goebert, Carl Wasmut
and James Gardner, Cleveland Clinic, Cleveland.

Stimulants for the Hyperactive Child?
George J. Lytton, and Mauricio Knobel, Kans
City, Kan.

Institutional Management of the Mentally Retarded.
Charles H. Carter, Sunland Training Center
Orlando, Orlando, Fla.

Management of Depression in General Medicine.
Joseph L. Bell, Hans Tauber, Albert C. Santy, a
Frank Pulito, New York.

Management of Insomnia.
Oscar Rozett, Fair Oaks Hospital Inc., Summit, N.

Drugs in Emotional Disorders: Past and Present.
Leo E. Hollister, Veterans Administration Hospit
Palo Alto, Calif.

**Methaminodiazepoxide-Autonomic Nervous System Rea
tion: The Control of Anxiety with Chemotherapy.**
Edwin Mc. N. Dunlop, Fuller Memorial Sanitariu
South Attleboro, Mass.

Management of Emotional Problems in a Geriatric Institution.
Edward A. Kent, Brooklyn Hebrew Home and Hospital for the Aged, Brooklyn, N. Y.

Community Readjustment of Former Mental Patients: A Five Year Study.
Else B. Kris, Research Unit, Manhattan Aftercare Clinic, New York.

Tranquilizers, Barbiturates and the Brain.
Harold E. Himwich, Galesburg State Research Hospital, Galesburg, Ill.

Section on Obstetrics and Gynecology

The representative to the Scientific Exhibit from the Section on Obstetrics and Gynecology is Frederick H. Falls, River Forest, Ill.

The Problem of Weight Control in Pregnancy.
Neel J. Price, George Washington University Hospital, Washington, D. C.

Methods for Determining Effects of Muscle Relaxants in Infants and Children.
Henry W. Baird III, Temple University School of Medicine, and St. Christopher's Hospital for Children, Philadelphia.

The Diagnosis and Treatment of Convulsive Disorders in Children.
Samuel Livingston and Lydia Pauli, Johns Hopkins Hospital, Baltimore.

Section on Physical Medicine

The representative to the Scientific Exhibit from the Section on Physical Medicine is Ralph E. Worden, Los Angeles.

Diagnosis of Hysterical Paralysis.
Ernest W. Johnson and Richard D. Burk, Ohio State University College of Medicine, Columbus, Ohio, and Ralph E. Worden, University of California School of Medicine, Los Angeles.

Physiologic Evaluation of Therapeutic Physical Agents.
David I. Abramson, Yvonne Bell, Samuel Tuck Jr., and Roscoe Mitchell, University of Illinois College of Medicine, Chicago.

Myositis.
W. C. Schaeffer, C. E. Rupe, R. E. Birk, and J. C. Sieracki, Henry Ford Hospital, Detroit.

Anatomical Localization of Common Vascular Brain Syndromes.
Alfred Ebel, Bronx, N. Y., Nicholas Panin, East Orange, N. J., and Milton Holtzman, Welfare Island, N. Y.

Electrophysiological Brace for Foot Drop in Hemiplegics.
W. T. Liberson, M. Dow, Veterans Administration Hospital, Hines, Ill., and H. J. Holmquest, Stritch School of Medicine of Loyola University, Chicago.

Stimulation Assistive Exercise (SAE) in Hemiplegia.
Harry T. Zankel, Veterans Administration Hospital, Durham, N. C.

Section on Preventive Medicine

The representative to the Scientific Exhibit from the Section on Preventive Medicine is Paul A. Davis, Akron, Ohio.

Who Has VD?
Willie G. Simpson and William F. Schwartz, Communicable Disease Center, Venereal Disease Branch, Atlanta, Ga.

Fluorescent Antibody Techniques in Veneral Disease Diagnosis.
William J. Brown, Willie G. Simpson, and Wilbur E. Deacon, Communicable Disease Center, Venereal Disease Branch, Atlanta, Ga.

Lung Cancer Prevention and the Physician.
Roald N. Grant, John F. W. King, and Daniel Horn, American Cancer Society, Inc., New York.

Oral Vaccines Containing Living Attenuated Poliomyelitis Viruses:
J. M. Ruegsegger, H. R. Cox, J. Daunas, V. Cabasso, and A. W. Moyer, Pearl River, N. Y.

Detection and Management of Chronic Diseases in Older People.
J. J. Van Gasse and W. M. Bain, Department of Health, Coquille, Ore.

Safe Meats Through Scientific Detection.
K. F. Johnson, United States Department of Agriculture, Washington, D. C.

Prevention and Control of Accidental Chemical Poisonings: Prevention Through Education.
Harold Jacobziner and Harry W. Raybin, New York City Department of Health, New York.

Section on Radiology

The representative to the Scientific Exhibit from the Section on Radiology is Richard H. Chamberlain, Philadelphia.

Angiocardiographic Findings in Congenital Heart Disease.
William T. Meszaros, Benjamin M. Gasul, Pedro Bicoff, Egbert H. Fell, Rene A. Arcilla, Joshua Lynfield, Magnus H. Agustsson, Zwi Steiger, and Lawrence L. Luan, Cook County Hospital, Chicago.

Evaluation of Radiological Criteria in the Diagnosis of Gastric Ulcer.
William H. Bachrach, Abraham Schneiderman, and Raleigh C. Bledsoe, Los Angeles.

Method of Analysis for Evaluation of Treatment in Oropharynx Cancers and Cancer of the Cervix.
Gilbert H. Fletcher, Paul M. Chau, and Eleanor J. MacDonald, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas.

Gastric Ulcer and Cancer, Roentgen Aspects.
Israel E. Kirsch, Veterans Administration Hospital, Hines, Ill.

Caffey's Disease: Ten Cases in Two Generations of One Family.
John P. Tampas, F. W. Van Buskirk, and O. S. Peterson Jr., University of Vermont College of Medicine, Burlington, Vt.

Recent Developments in Oral Cholecystography.
Walter M. Whitehouse, Robert Rapp and Howard E. Fink Jr., University of Michigan Medical School and Veterans Administration Hospital, Ann Arbor, Mich.

Diagnosis in Patient with Stroke.
Robert A. Kuhn, All Souls Hospital, Morristown, N. J.

Systemic Disease as Manifested in X-rays of the Hands and Wrists.
Thurman Gillespy Jr., Irwin I. Kricheff, Anthony DePalma, Russell Miller, and James Hunter, Philadelphia General Hospital, Philadelphia.

Section on General Surgery

The representative to the Scientific Exhibit from the Section on General Surgery is Julian Johnson, Philadelphia.

Antineoplastic Effects of Fluoropyrimidines.
A. R. Curreri, C. Heidelberger and F. J. Ansfield, University of Wisconsin School of Medicine, Madison, Wis., and R. Duschinsky and R. J. Schnitzer, Hoffmann-La Roche Inc., Nutley, N. J.

The Differential Diagnosis of Isolated Bone Lesions Containing Giant Cells.
J. I. KENDRICK, GEORGE S. PHALEN, and L. J. MCCORMACK, Cleveland Clinic, Cleveland.

The Infant's Hip—Normal or Dysplastic?
CHARLES T. RYDER, JOHN CAFFEY, and GILBERT MELLIN, Columbia-Presbyterian Medical Center, New York.

Surgical Fixation of Small Important Bone Fragments (Ankle and Elbow) with the Hookplate.
WILHELM A. ZUELZER, DeWitt Army Hospital, Fort Belvoir, Va.

Bone and Joint Changes Following Burns: A Roentgenographic Study.
E. BURKE EVANS and JAMES R. SMITH, University of Texas Medical Branch, Galveston, Texas.

Un-United Fractures of the Carpal Navicular.
MIHRAN O. TACHDJIAN, Ireland Army Hospital, Ft. Knox, Ky., PHILIP H. DAVIS, Burlington, Vt., and COURSEN B. CONKLIN, Albuquerque, N. Mex.

Shoulder Arthrography.
ROBERT L. SAMILSON, ROBERT RAPHAEL, LAWRENCE POST, and CHARLES NOONAN, University of California School of Medicine, San Francisco.

Congenital Kyphosis: The Genesis of Microspondyly.
W. H. AKESON and D. S. KELLAM, University of North Carolina School of Medicine, Chapel Hill, N. C.

Section on Pathology and Physiology

The Section on Pathology and Physiology is cooperating in the Special Exhibit on Fresh Tissue Pathology. The representative to the Scientific Exhibit is SAMUEL A. LEVINSON, Chicago.

Estrogens and Components of Coagulation.
J. F. JOHNSON and N. J. FURIOSI, Wayne State University College of Medicine, Detroit.

The Pancreas in Human and Experimental Diabetes.
B. W. VOLK and S. S. LAZARUS, Isaac Albert Research Institute, Brooklyn.

Certification of Medical Technologists.
LALL G. MONTGOMERY and RUTH DRUMMOND, American Society of Clinical Pathologists, Muncie, Ind.

Pathology of Major Pulmonary Diseases as Demonstrated by Fume Fixation.
WILLIAM HENTEL, A. N. LONGFIELD and HOLLIS BOHEN, Veterans Administration Hospital, Albuquerque, N. Mex., and B. J. BLUMENTHAL, Veterans Administration Hospital, Houston, Texas.

Cellular Physiology of Aging: Various Expressions of a Biological Process.
LUTHER L. TERRY and BERNARD STREHLER, National Heart Institute, Bethesda, Md.

Cancer Cell Detection by Millipore Technique.
HERMAN BERNHARDT, JOSEPH M. YOUNG and ROBERT GOURLEY, Veterans Administration Hospital, Memphis, Tenn.

Electrical Device to Demonstrate the Blood Clotting Mechanism.
ELEMER GABRIELI and WILLIAM C. SLEIGHT, Millard Fillmore Research Institute, Buffalo.

Bronchopulmonary Mycosis: Twenty Year Observation Following Primary Occurrence.
BRENTON M. HAMIL, W. R. EYLER, J. W. REBUCK, and G. A. LOGRIPPO, Henry Ford Hospital, Detroit.

Multicentric Carcinogenesis in the Human Liver.
HANS ELIAS, Chicago Medical School, Chicago.

Human Skin Windows and the Functions of White Blood Cells.
JOHN W. REBUCK, RAYMOND W. MONTO, and ROBERT J. PRIEST, Henry Ford Hospital, Detroit.

Rapid Clinical Screening for Lung Cancer.
WILLIAM UMIKER and DONALD KORST, Veterans Administration Hospital, Ann Arbor, Mich.

Section on Pediatrics

The representative to the Scientific Exhibit from the Section on Pediatrics is F. THOMAS MITCHELL, Memphis, Tenn.

Brain Abnormalities Observed in Children with Mental Retardation and Other Forms of Cerebral Palsy: Means of Diagnosis and Treatment.
WILLIAM T. GRANT, Pasadena, Calif.

The Conduction System in Cardiac Surgery.
MAURICE LEV, WILLIAM L. RIKER, ARTHUR DEBOER, THOMAS G. BAFFES, and WILLIS J. POTTS, Children's Memorial Hospital, Chicago.

Treatment of Constipation in Infants and Children.
EMANUEL DUBOW, Beekman Downtown Hospital, New York.

Chemistry, Chromosomes, and Congenital Anomalies.
VIRGINIA APGAR, The National Foundation, New York.

The Imperfect Child: Etiological Factors, Incidence, and Therapeutic Modalities.
RICHARD B. STARK, CARL T. JAVERT, ELISE RENNING and CLAYTON R. DEHAAN, St. Luke's Hospital, and the Well Born Foundation, New York.

Prevention of Recurrences of Rheumatic Fever.
ALAN C. SIEGEL and ELOISE JOHNSON, Children's Memorial Hospital, Northwestern University Medical School, Chicago.

Relocation and Recession of the Enlarged Clitoris: An Alternative to Amputation.
JOHN K. LATTIMER, Babies Hospital, Columbia University College of Physicians and Surgeons, New York.

"Holistic" Management of the Allergic Child.
JOHN P. MCGOVERN, THEODORE J. HAYWOOD, GILBERT BARKIN, KEMAL OZKARAGOZ, and ALBERT HENSEL JR., Baylor University College of Medicine, Houston, Texas.

Infantile Eczema: Pathology and Therapy.
EMILIA SEDLIS and PHILIP PROSE, New York University College of Medicine and Bellevue Medical Center, New York.

The Control of the Organic Hyperkinetic Behavior Syndrome in the Elementary School Child.
V. RICHARD ZARLING and JOE HOGAN, Minneapolis.

Help and Hope for the Dystrophic Patient.
ADE T. MILHORAT, New York.

Neurofibromatosis in Children.
HAROLD W. DARGEON, CHARLOTTE TAN, and ROSA ECHEVARRIA, Memorial Center for Cancer and Allied Diseases, New York.

Infections in Private Pediatric Practice.
FRANK M. RIPBERGER, ROBERT H. ANDERSON and RICHARD E. PALMER, Alexandria Hospital, Alexandria, Va.

The Megacystis Syndrome.
Albert J. Paquin Jr., University of Virginia School of Medicine, Charlottesville, Va., Victor F. Marshall, and John McGovern, Cornell University Medical College, New York.

Chemotherapy of Testis Tumors.
Willet F. Whitmore Jr., Min-Chiu Li, Robert Golbey, and Harry Grabstald, Memorial Center for Cancer and Allied Diseases, New York.

Postoperative Contractures of the Vesical Neck: Clinical and Experimental Studies.
Laurence F. Greene, H. P. Robinson and J. C. Campbell, Mayo Clinic and Mayo Foundation, Rochester, Minn.

Seminal Vesicles: Before and After Open Prostatectomy.
Jasper H. Arnold, Baylor University College of Medicine, Houston, Texas.

A New One-Stage Operation for Hypospadias.
Stanley B. Braham, George F. Crikelair, and Sam Knappenberger, Columbia University College of Physicians and Surgeons, New York.

Undescended Testis: Surgical Anatomy of Spermatic Surgical Triangles and Lateral Spermatic Ligament.
Robert J. Prentiss, Charles J. Weickgenant, James J. Moses, and Donald B. Frazier, San Diego County Hospital, San Diego, Calif.

Classification of Urinary Tract Bacteria by Enzyme Activity.
Harry Seneca, J. K. Lattimer, H. H. Zinsser, and O. K. Troc, Columbia University College of Physicians and Surgeons and Presbyterian Hospital, New York.

Anti-spermatozoal Immunologic Factors in the Etiology of Infertility.
Edward T. Tyler, Shanta Rao, Sheldon Segal, Albert Tyler, and N. Nakabayaski, University of California School of Medicine, Los Angeles.

The Vesical Herald Patch.
Meyer M. Melicow and Aurelio C. Uson, Squier Urological Clinic, Columbia-Presbyterian Medical Center, New York.

Section on Miscellaneous Topics

Medical Pathfinders.
John A. Mirt and Clara Mai Rutherford, Illinois State Medical Society, Chicago.

New Ways in Teaching Brain Anatomy: The Transparent Brain.
Ph. Schwartz and I. Guneral, Warren State Hospital, Warren, Pa.

Michigan's Program in Postgraduate Medicine.
John M. Sheldon, Harry A. Towsley, Park W. Willis III, George H. Lowrey, C. Thomas Flotte, and Samuel J. Behrman, University of Michigan Medical School, Ann Arbor, Mich.

Disability: Dilemma and Decision; The Physician's Part in the Determination of Disabilty.
William Roemmich, Social Security Administration, Bureau of Old-Age and Survivors Insurance, Baltimore.

Medicine as a Career.
Walter S. Wiggins and Catherine Hayes, Council on Medical Education and Hospitals, American Medical Association, Chicago.

Visual Aids in Medical Presentations.
Hunter H. Romaine and John Goeller, New York Eye and Ear Infirmary, New York.

Educational Activities.
George W. Stephenson, American College of Surgeons, Chicago.

American Association of Blood Bank Services.
William P. Murphy Jr., American Association of Blood Banks, Miami, Fla.

Automobile Seat Belts: A Means to Reduce Severity of Injury in Auto Accidents.
Howard N. Schulz, Committee on Medical Aspects of Automobile Injuries and Deaths, American Medical Association, Chicago.

How Can I Take Part in the Medical Meeting?
George F. Schmitt and Franklin J. Evans, University of Miami School of Medicine, Miami, Fla.

Fluoridation: A Statement by the American Medical Association.
Norman F. Gerrie, Public Health Service, Washington, D. C.

American Hospital Association.
Joseph R. Anderson, American Hospital Association, Chicago.

Progressive Patient Care.
Edward T. Thompson, E. Josephine Strachan and Donald A. Knowles, U. S. Public Health Service, Washington, D. C.

Summary of Fiscal and Enrollment Data on Blue Shield Prepayment Medical Care Plans.
Lawrence C. Wells, Blue Shield Medical Care Plan, Chicago.

The Family Room of Tomorrow: A Family Fallout Shelter.
Frank W. Barton, U. S. Office of Civil and Defense Mobilization, Council on National Security, American Medical Association, Chicago.

A Rehabilitation Center Serves a Community.
Dean W. Roberts, Jayne Shover, and Florence Stattel, National Society for Crippled Children and Adults, Inc., Chicago, and Ezelle B. Kerrigan, The Crippled Children's Society, Miami, Fla.

Standard Nomenclature.
Adaline C. Hayden, American Medical Association, Chicago, and Edward T. Thompson, Washington, D. C.

Alcoholism: Alcoholism Is Your Business.
Marvin A. Block, Buffalo, Committee on Alcoholism, American Medical Association, Chicago.

Sunlight and the Skin.
Veronica L. Conley, Committee on Cosmetics, American Medical Association, Chicago.

Group Practice Survey.
George W. Cooley, Council on Medical Service, Robert S. Condie, American Association Medical Clinics, and M. W. Shearer, National Association of Clinic Managers, Chicago.

Techniques of Partial Nephrectomy.
William M. Parry, Veterans Administration Hospital, Joseph F. Finelli, State University of New York, Upstate Medical Center, Syracuse.

The Role of the Pancreas in Peptic Ulceration.
Harry A. Oberhelman Jr., T. S. Nelsen, L. R. Dragstedt, L. R. Dragstedt II, A. N. Johnson Jr., E. R. Singer, E. Paloyan, and H. B. Greenlee, The University of Chicago, The School of Medicine, Chicago.

Antrectomy with Vagectomy for Chronic Duodenal Ulcer.
Louis T. Palumbo, Wendell S. Sharpe, Donald J. Lulu, and Raymond Vespa, Veterans Administration Center, Des Moines, Iowa.

How to Run Clean Operating Rooms.
Ralph Adams, Burke Fahlman, and Jacqueline Lord, Huggins Hospital, Wolfeboro, N. H.

Stricture of the Common Bile Duct: Etiology, Prevention, Surgical Treatment.
Harwell Wilson and Edward H. Stober, University of Tennessee College of Medicine, Memphis, Tenn.

Oxyphenbutazone: A New Anti-inflammatory Agent—Evaluation in Surgical Lesions.
James F. Connell Jr., Robert Wallace, Norman Kleinman, and Louis M. Rousselot, St. Vincent's Hospital and New York University College of Medicine, New York.

Steering Wheel Injuries to the Chest.
William G. Pace, Charles V. Meckstroth, and Karl P. Klassen, Ohio State University Health Center, Columbus, Ohio.

Selective Visceral Arteriography.
John R. Derrick, C. Agnew, and R. N. Cooley, Medical Branch University of Texas, Galveston, Texas.

Complications of Gastric Resection: Diagnosis and Management.
James D. Hardy, Jaré L. Barkley, and John E. Hoopes, University of Mississippi Medical Center, Jackson, Miss.

Evaluation of a New Absorbable Hemostatic Material Prepared from Oxidized Regenerated Cellulose.
Elliott S. Hurwitt, George F. Gitlitz, John Henderson, and Geoffrey H. Lord, Montefiore Hospital, New York, and Johnson and Johnson Research Foundation, New Brunswick, N. J.

Surgical Treatment of Renal Hypertension.
George C. Morris Jr., Michael E. DeBakey, Denton A. Cooley, and E. Stanley Crawford, Baylor University College of Medicine, Houston, Texas.

A New Technique for the Repair of Inguinal and Incisional Hernias.
Francis C. Usher and John L. Ochsner, Baylor University College of Medicine, Houston, Texas.

Pseudomembranous (Micrococcal) Enterocolitis: Etiology, Mechanism and Therapy of the Disease.
John Van Prohaska, Farrell Mock, Ruth Collins, and William Baker, The University of Chicago, The School of Medicine, Chicago.

Bronchogenic Carcinoma.
Robert R. Shaw, Donald L. Paulson, and John L. Kee Jr., Baylor University Medical Center, Dallas, Texas.

Transseptal Left Heart Catheterization.
John Ross Jr., Eugene Braunwald, and Andrew G. Morrow, National Heart Institute, Bethesda, Md.

Esophageal Diverticulum.
David P. Boyd and Robert E. Wise, Lahey Clinic, Boston.

Stress and Decreased Resistance to Cancer.
Gerald O. McDonald and Warren H. Cole, University of Illinois College of Medicine, Chicago.

Contrast Visualization of the Vascular System: Indications and Techniques.
Daniel F. Casten, Marvin Chirls, and Alex Norman, Hospital for Joint Diseases and St. Clare's Hospital, New York.

The Diagnosis and Management of Malignant Melanoma.
Gordon McNeer, Robert Booher, Theodore Miller, C. McPeak, R. Brasfield, Lemuel Bowden, Joseph Fortner, and Walter Lawrence, Memorial Center for Cancer and Allied Diseases, New York.

Treatment of Internal Mammary Nodes with Radioisotopes.
Richard D. Brasfield and Ulrich K. Henschke, Memorial Center for Cancer and Allied Diseases, New York.

A Skin Bank for Autografts.
Irving Feller and Marion DeWeese, University of Michigan Medical Center, Ann Arbor, Mich.

Heterograft Skin: A Biologic Dressing.
Irvin H. Sokolic, Alex W. Ulin, and John M. Howard, Albert Einstein Medical Center, Southern Division and Hahnemann Medical College and Hospital, Philadelphia.

Fractures of the Mandible.
Robin Anderson and Eldon R. Dykes, Cleveland Clinic, Cleveland.

The Application of Plastic Surgery Principles in the Treatment of Facial Injuries.
Thomas John Zaydon, University of Miami School of Medicine, Miami, Fla., and James Barrett Brown, Washington University School of Medicine, St. Louis.

Clinical Experiences with a New Hemostatic Cellulose.
R. W. Postlethwait and John Henderson, Veterans Administration Hospital, Durham, N. C.

Tetracycline in Tumors.
Benedict R. Walske and John F. McLeay, Creighton University School of Medicine, and Richard E. Ogborn, Veterans Administration Hospital, Omaha.

Obstructive Lesions of the Pancreatic Ductal System.
Brock E. Brush, Joseph L. Ponka and R. O. Antoni, Henry Ford Hospital, Detroit.

Section on Urology

The representative to the Scientific Exhibit from the Section on Urology is E. F. Poutasse, Cleveland.

Renal Hypertension.
Thomas A. Stamey, Irwin J. Nudelman, and Frederic N. Schwentker, Brady Urological Institute, The Johns Hopkins Hospital, Baltimore.

Anastomosis of the Vas Deferens: Principles and Presentation of an Improved Technique.
Stanwood S. Schmidt, Eureka, Calif.

INDUSTRIAL EXHIBITORS——109th ANNUAL MEETING

	Booth Numbers
Abbott Laboratories	E-26, 27, 28, 29, F-26, 27, 28, 29
Aeroplast Corporation	N-6
Air-Shields, Inc.	J-50
Alcon Laboratories, Inc.	B-43
American Cyanamid Company (Surgical Products Division)	D-53
American Cystoscope Makers, Inc.	J-57, 59
American Medical Association Publications	N-11, 13, 15
American Medical Education Foundation	E-21
American Hospital Supply Corporation	I-10
American Sterilizer Company	D-50, 52
Ames Company, Inc.	H-16, 18
Amfre-Grant, Inc.	N-17
Appleton-Century-Crofts, Inc.	C-23
Armour Pharmaceutical Company, The	E-36, 38
Association of American University Presses	N-19
Audio-Digest Foundation	F-37
Aveeno Corporation	D-6
Ayerst Laboratories	B-31, 32, 33, 35, 37, 39
Barton Manufacturing Company	C-25
Baum, W. A., Co., Inc.	G-47
Bausch & Lomb Optical Company	E-50
Baxter Laboratories, Inc.	H-56, 58
Beck-Lee Corporation	F-59
Becton, Dickinson & Company	E-47, 49
Bell & Howell Company	N-4
Beltone Hearing Aid Company	K-1
Best Foods Division of Corn Products Company	I-25, 27
Blakiston Division of McGraw-Hill Book Company	G-57, 59
Borcherdt Company	D-20
Breck, John H., Inc.	D-53
Breon, George A., & Company	I-37, 39
Brewer & Company, Inc.	O-5
Bristol Laboratories	H-33, 35
Bruning, Charles, Co., Inc.	B-9, 10
Burdick Corporation, The	G-2; H-1, 2
Burns Cuboid Company	E-2
Burroughs Corporation	E-9
Burroughs Wellcome & Co. (U. S. A.) Inc.	J-30, 32
Burton Manufacturing Company (M D L Division)	N-7
Burton, Parsons & Company	A-20
Calgon Company	A-1
Cambridge Instrument Co., Inc.	C-11
Cameron Surgical Instruments Company	B-18
S. H. Camp & Company	C-15
Canada Dry Corporation	E-56
Cardiotron, E. P. L., Inc.	B-5
Carnation Company	D-60; E-61
Chattanooga Pharmacal Company	A-12
Chicago Pharmacal Company	H-50
Chicago Reference Book Company	O-4
Chilean Iodine Educational Bureau, Inc.	J-20
Christian Medical Society	H-63
Church & Dwight Company, Inc.	E-58
Ciba Pharmaceutical Products, Inc.	F-20, 22, 31, 33, 35; E-30, 32, 34
Clark-O'Neill, Inc.	B-52
Coca-Cola Company, The	G-1; F-1, 2
Colgate-Palmolive Company	N-16
Collins, Warren E., Inc.	C-1
Colwell Publishing Company	H-60
Compass Travel Bureau, Inc.	A-11
Coreco Research Corporation	K-6
Cream of Wheat Corporation, The	G-55
Cutter Laboratories	D-48
Dalzo, Inc.	A-16
Dara Products	O-8
Darwin Laboratories	B-19
Davies, Rose & Co., Ltd.	J-1
Davis, F. A., Company	I-57, 59
DePuy Manufacturing Company, Inc.	I-60
DeVilbiss Company	E-51
Desitin Chemical Company	I-1
Devereux Schools	G-34
Dictograph Products	O-19
Dictaphone Corporation	C-5, 7
Dine, Lester A., Company	E-13
Doak Pharmacal Co., Inc.	A-13
Doho Chemical Corporation	E-20, 22
Dome Chemicals, Inc.	F-12
Duke Laboratories, Inc.	H-39
Eastman Kodak Company	D-8, 10, 12
Eaton Laboratories	I-16, 17, 18, 19
Edison, Thomas A., Industries	C-50, 52
Eisele & Company	F-51
Emerson, J. H., Company	B-7
Encyclopaedia Britannica, Inc.	J-39
Endo Laboratories, Inc.	F-41, 43
Engelhard Industries, Inc.	H-61; G-60, 61
Epsco Worcester Division of Epsco, Inc.	J-38
Ethicon, Inc.	G-54, 56, 58; H-55, 57, 59
Excerpta Medica Foundation	O-12, 14
Fisher-Stevens, Inc.	I-63
Fischer, H. G., & Company	A-17
Flint Eaton & Company	H-52, 54
Florida Brace Corporation	O-10
Fleet, C. B., Co., Inc.	F-46, 48
Foregger Company, Inc., The	C-53
Fougera, E., & Company, Inc.	D-4; H-13
Geigy Pharmaceuticals	I-26, 28; J-27, 29
General Electric Company, X-Ray Dept.	C-2; D-1
General Foods Corporation	C-45, 47, 49
Gerber Products Company	H-11
Geriatric Pharmaceutical Corp.	O-9
Glenbrook Laboratories	E-48
Golden Guernsey, Inc.	B-45
Grant, R. D., Company, The	F-63
Gray Manufacturing Company	J-11, 13
Great Books of the Western World	N-3
Grune & Stratton, Inc.	D-47, 49
Hamilton Mfg. Company	J-56, 58
Harvey, G. F., Company, Inc., The	E-7; J-34
Health Insurance Council	B-54
Heinz, H. J., & Company	J-7, 9
Hoeber, Paul B., Inc.	F-47, 49
Holland-Rantos Co., Inc.	C-37, 39
Hollister-Stier Laboratories, Inc.	C-9
Identical Form, Inc.	H-37
Ille Electric Corporation	A-14
International Business Machines Corp.	G-51, 53
International College of Surgeons	N-2
International Medical Research Corp.	O-3
Ives-Cameron Company	H-5, 7
Jacuzzi Research, Inc.	B-48
Jobst Institute, Inc., The	N-5
Johnson & Johnson	G-46, 48; H-47, 49
Jones Metabolism Equipment Company	B-14
Kastoff, Inc.	O-7
Keeler Optical Products, Inc.	B-46
Kendall Company, Division of Bauer & Black	D-54, 56, 58
Key Corporation	F-57
Kidde Mfg. Company	G-49
Kimberly-Clark Corporation	E-53
Knoll Pharmaceutical Company	E-46
Knox, Charles B., Gelatine Co., Inc.	B-30
Lafayette Pharmacal, Inc.	I-55

THE INDUSTRIAL EXHIBITION

109th A. M. A. Annual Meeting

June 13-17, 1960 • Miami Beach Auditorium & Exhibition Hall

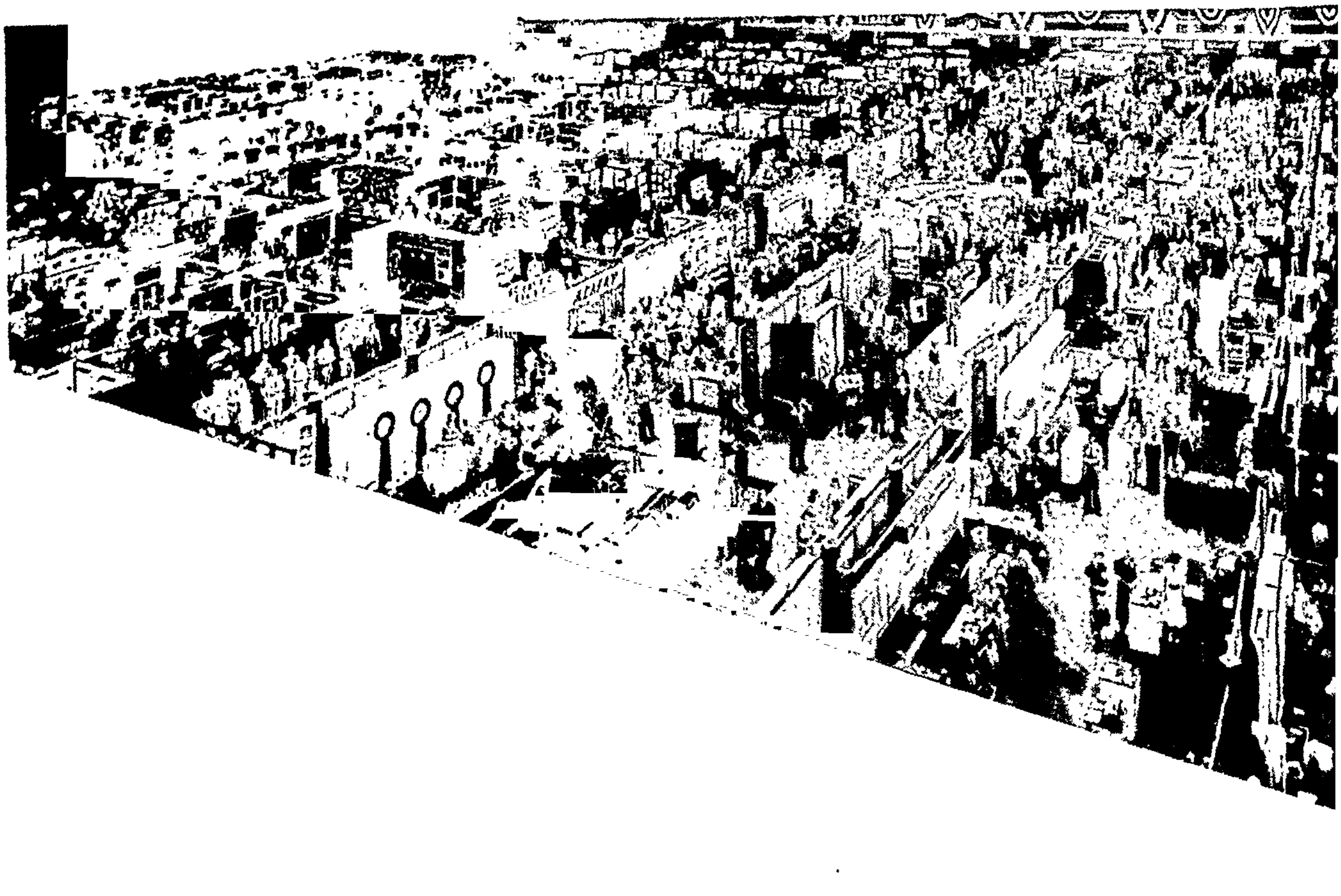
The Industrial Exhibits at the Miami Beach Meeting will provide a quick review of the new developmen in medicine.

The visiting physician will have an excellent opportunity to examine new ideas and new methods as w as to review familiar products and new applications that have been developed.

From Monday to Friday, June 13 to 17, about 300 industrial exhibitors will present products and services the field of medicine. Well-trained representatives of each company will answer your most technical qu tions, helping in every way to make your practice of medicine more effective and efficient.

The Industrial Exhibits will be open from 8:30 a. m. to 5:30 p. m. each day of the meeting, closing Frid at 12:00 noon. On June 14, 15, and 16 the Industrial Exhibits, as well as all other activities of the Meetin will be open for physicians only until noon.

We look forward to seeing you in Miami Beach and to your making full use of the values the Industri Exhibits offer you.



REPORTS OF OFFICERS

REPORT OF BOARD OF TRUSTEES

To the Members of the House of Delegates of the American Medical Association:

The following report of the Board of Trustees is respectfully submitted.

Financial Statement

The official 1959 financial reports of the Association's Accountants appear as part of this report.

Report on Matters Referred by House of Delegates

American Medical Association Publications: At its Dallas meeting (December 1959) the House of Delegates adopted Resolution #2, introduced by Dr. Scarcello of Massachusetts, which requested the Board of Trustees to investigate the advisability and feasibility of making the various publications of the A. M. A. available to libraries of constituent state and local medical societies, of approved medical schools, and of accredited hospitals, without charge or at reduced cost.

At the present time the following libraries are receiving complimentary copies of the *A. M. A. News:*

Constitutent state medical societies—53
Component medical societies—197
Approved medical schools—89
Accredited hospitals—approximately 3,000

Approximately 400 to 500 of these libraries are receiving all other A. M. A. publications by virtue of paid subscriptions.

Inasmuch as a change in this policy would result in a considerable loss of revenue to the Association, the Board of Trustees recommends that no change be made in the present policy of distribution of A. M. A. publications to libraries.

Referrals: Other matters from the House of Delegates meeting in Dallas have been referred to appropriate councils, committees and departments for study. As soon as reports are available from these groups, they will be transmitted to the House of Delegates.

Change in Titles for Councils

At its meeting in February the Board of Trustees changed the title of the Council on Industrial Health to Council on Occupational Health, and that of the Council on National Defense to Council on National Security.

The Board further defined the scope and functions of the Council on National Security as outlined in the following statement:

> Realizing the complexities of the organization of the federal government and the A. M. A., as well as the changing concepts of our national defense and national strategy.
>
> (*a*) The scope and purpose of the Council on National Defense is to provide advice and assistance to the Board of Trustees and to the medical profession on all matters involving the medical and health aspects of the national security, particularly as such national security pertains to the utilization, mobilization and coordination of medical and health resources.
>
> (*b*) In the discharge of these responsibilities, the Council shall maintain effective liaison with other councils, committees and others within the Association and shall refer appropriate scientific and professional problems to the proper groups for study, advice and recommendation.
>
> (*c*) Liaison shall also be maintained with government and nongovernment departments, agencies and associations on matters involving medical and health problems and activities in national security.

Commission on Costs of Medical Care

A Commission on the Costs of Medical Care has been established by the Board of Trustees. The Commission will study all medical care costs, including doctors' fees, hospital charges, nursing costs, drug expenditures, and health insurance premiums. In conducting this study, the Commission will consult with economists, health insurers, pre-payment plans, hospital representatives, a cross section of patients, and others whose knowledge and opinions will be helpful.

Mayo Brothers

The Board of Trustees received a request from the Citizens Committee in Support of a Commemorative Stamp for the Mayo Brothers for endorsement of its efforts in this area.

Inasmuch as both William and Charles Mayo have been presidents of the America Medical Association, the Board voted to endorse these activities and in accordance with a request from the Citizens Committee, sent a letter to the Postmaster General in this regard.

Scope, Objectives, and Functions of Occupational Health Programs

In June 1957 the House of Delegates approved of a statement on "Scope, Objectives, and Functions of Occupational Health Programs" developed by the Council on Industrial Health (now the Council on Occupational Health) and approved by the Board of Trustees.

The following revision of the statement is submitted for study by the House of Delegates, with the recommendation of the Board of Trustees that it be adopted:

Scope, Objectives, and Functions of Occupational Health Programs

INTRODUCTION

The term "occupational health program," as used in this statement, means a program provided by management to deal constructively with the health of employees in relation to their work.

The term "occupational medicine" means that branch of medicine practiced by physicians in meeting medical problems and needs under occupational health programs.

Some employers, in the middle of the 19th century, established medical services for their employees in areas where satisfactory medical services were not readily available. Since 1911, workmen's compensation laws requiring employers to compensate employees or their heirs for occupational disability or death and to provide medical care for occupationally injured employees have been enacted in all states. In

	Booth Numbers
Lakeside Laboratories, Inc.	J-40, 42
Lea & Febiger	B-41, 42
Lederle Laboratories Division, American Cyanamid Co.	A-2, 4; B-25, 27
Leeming, Thomas, & Co., Inc.	J-5
Lilly, Eli, and Company	H-40, 42, 46, 48; I-41, 43, 47, 49
Lippincott, J. B., Company	J-46, 48
Little, Brown & Company	I-55
Lloyd Brothers, Inc.	I-5; J-25
Loma Linda Food Company	J-36; O-15
Lo-Sodium Dairy Products Corp.	O-17
Luzier's, Inc.	J-2
Macmillan Company, The	I-6, 8
Mahon, Thomas J. Company	H-9
Maico Electronics, Inc.	B-29
Mallinckrodt Chemical Works	B-44
Maltbie Laboratories, Division of Wallace & Tiernan, Inc.	F-39; J-21, 23
Manhattan Uniform Company	F-61
Marco & Son	O-11
Marion Laboratories, Inc.	N-8
Massachusetts Indemnity & Life Insurance Co.	F-10
Massengill, S. E., Company, The	C-1; K-2
Mattern X-Ray Division of Land-Air, Inc.	F-60
McCarty's, Inc.	K-5, 7
McKesson Appliance Company	E-11
McNeil Laboratories, Inc.	I-30, 31, 32, 33, 35
Mead Johnson and Company	D-30, 32, 34, 36, 38, 40, 42; E-31, 33, 35, 37, 39, 41, 43; J-26, 28
Medco Products Company, Inc.	E-5
Medical Plastics Laboratory	I-61
Medical Protective Company, The	G-50
Merck Sharp & Dohme	F-30, 32, 34, 36, 38, 40, 42; G-31, 33, 35, 37, 39, 41, 43
Merrell, Wm. S. Company, The	D-2; E-1
Merrill Lynch, Pierce, Fenner & Smith	B-1
Miles Laboratories, Inc.	A-6, 8
Miles Reproducer Company, Inc.	N-14
Milex Products	B-50
Miller Surgical Company	I-58
Minnesota Mining & Manufacturing	F-21, 23, 25
Modern Medicine	J-55
Monaghan Company, J. J., Inc.	I-50
Mosby, C. V. Company, The	J-16, 18
Mutual of Omaha	C-51
National Cash Register Company, The	J-22, 24
National Cylinder Gas Division Chemetron Corp.	I-52
National Drug Company, The	C-46, 48
National Federation of Catholic Physicians' Guilds	B-11
National Live Stock and Meat Board	F-54
Nega-File Company	O-18
Nordson Pharmaceutical Laboratories	G-40, 42
North American Phillips Company, Inc.	B-16, 17
Lydia O'Leary, Inc.	J-52
Organon, Inc.	F-4
Ortho Pharmaceutical Corporation	G-10, 11, 12, 13
Orthopedic Frame Company	A-19
Oster, John, Manufacturing Company	B-51
Otarian Listener Corporation	A-18
Ovaltine Food Products Division of The Wander Company	H-41, 43
Oxford University Press	B-4
Parke Davis and Company	C-30, 32, 34, 36; D-31, 33, 35, 37
Pelton and Crane Company	H-21
Pepperidge Farm, Inc.	O-13
Pepsi-Cola Company	J-4, 6, 8, 10, 12
Personal Products Corporation	F-50, 52
Pet Milk Company	B-20, 21
Pfizer Laboratories	H-4, 6, 8, 10, 12; I-5, 7, 9, 11, 13
Pharmacia Laboratories, Inc.	D-51
Picker X-Ray Corporation	N-1
Pitman-Moore Company	B-34
Plough, Inc.	C-3
Postgraduate Medicine	O-1
Poythress, Wm. P., and Company, Inc.	O-16
Prior, W. F. Company	H-31, 33
Procter & Gamble	G-36, 38
Professional Life & Casualty Company	K-21
Publishers' Authorized Bindery Service, Ltd.	B-45
Purdue Frederick Company, The	B-22; D-46; H-17, 19; O-2
Pyramid Rubber Company, The	F-6, 8
Radium Chemical Company, Inc.	E-43
Reed and Carnrick	B-13
Revlon, Inc.	F-56, 58
Revlon, Inc., Thayer Laboratories Division	B-47
Rexall Drug Company	E-52, 54
Richards Manufacturing Company	A-7
Riker Laboratories, Inc.	E-23, 25
Ritter Company, Inc.	I-51, 53
Robins, A. H. Company, Inc.	E-16, 18; F-17, 19
Roche Laboratories	E-4, 6, 8, 10, 12; F-5, 7, 9, 11, 13
Roerig, J. B. and Company	G-17, 19, 21, 23, 25, 27, 29
Rorer, William H., Inc.	J-47, 49
Ross Laboratories	C-21
Sanborn Company	J-40, 42
Sandoz Pharmaceuticals	D-22; I-34
Sanna Dairies, Inc.	B-2, 3
Saunders, W. B. Company	H-32, 34, 36, 38
SchenLabs Pharmaceuticals, Inc.	E-40, 42
Schering Corporation	C-20, 22, 24, 26, 28; D-21, 23, 25, 27, 29
Schieffelin and Company	C-13
Schmid, Julius, Inc.	D-16, 18
Scholl Manufacturing Company, Inc., The	B-6
Sealy, Inc.	E-57, 59
Searle, G. D. and Company	C-16, 18; D-17, 19
Seven-Up Company, The	J-41, 43
Shampaine Company	E-60
Simmons Company	I-21, 23
Smith Dorsey, Division of The Wander Company	E-24
Smith Kline and French Laboratories	H-18, 20; I-27
Smith, Miller and Patch, Inc.	I-35
Squibb, E. R. and Sons	G-22, 24, 26, 28; H-23, 25, 27; I-2
Stanton Scientific Equipment Company	I-48
Stephenson Corporation	N-10
Strasenburgh, R. J. Company	A-3
Stuart Company, The	B-23
Sunkist Growers, Inc.	G-6, 8
Swift and Company	F-22
Syntex Chemical Company, Inc.	I-20
Tailby-Nason Company, Inc.	J-61
Tampax, Incorporated	I-22, 24
Taylor Instrument Companies	J-17, 19
Testagar and Company, Inc.	J-54
Titmus Optical Company	N-12
Tru-Eze Manufacturing Company, Inc.	A-10
U. S. Vitamin & Pharmaceutical Corp.	G-16, 18, 20
Upjohn Company, The	C-54, 55, 56, 57, 58, 59, 60, 61; D-55, 57, 59, 61
Veratex Professional Products Company	N-9
Walgreen Drug Stores	E-17, 19
Walker Laboratories, Inc.	D 23
Wallace Laboratories	B-23, 24, 26, 28; D-26, 28; G-30, 32
Wampole Laboratories	A-9; G-9; J-51
Warner-Chilcott Laboratories	C-38, 40, 42; D-39, 41, 43
Warren-Teed Products Company	J-53
Welch Allyn, Inc.	D-24
Wesson Oil Company, The	I-35
Westinghouse Electric Corporation, X-Ray Dept.	F-53, 55
Westwood Pharmaceuticals	B-33, 43
White Laboratories, Inc.	J-31, 33, 35, 37
Williams and Wilkins Company, The	G-5, 7
Winthrop Laboratories	H-20, 22, 24, 26
Woodward Medical Personnel Bureau	F-24
World Medical Association, The	O-4
Wyeth Laboratories	C-4, 6, 8, 10, 12; D-5, 7, 9, 11, 13
Year Book Publishers, Inc., The	F-16, 18
Yorke Publishing Company	G-52

limb or to relieve suffering until placed under the care of his personal physician.

(2) For minor disorders, first aid or palliative treatment may be given if the condition is one for which the employee would not reasonably be expected to seek the attention of his personal physician, or to enable the employee to complete his current work shift before consulting his personal physician. Requests for repetitive treatment of nonoccupational disorders should be discouraged and individuals requesting such should be referred to their personal physician.

Every employee should be encouraged to have a personal physician. The health interests of employees are best served by communication and cooperation between their personal physicians and physicians participating in occupational health programs. This helps assure their continuation in or prompt restoration to suitable employement.

4. Immunization programs.
   An employer may properly make immunization procedures available to his employees under the principles set forth in the "Guide for Industrial Immunization Programs" (J. A. M. A. 171:2097-2098 [Dec. 12] 1959).
5. Medical records.
   The maintenance of accurate and complete medical records of each employee from the time of his first examination or treatment is a basic requirement. The confidential character of these records, including the results of health examinations, should be rigidly observed by all members of the occupational health staff. Such records should remain in the exclusive custody and control of the medical personnel. Disclosure of information from an employee's health record should not be made without his consent, except as required by law.
6. Health education and counselling.
   Occupational health personnel should educate employees in personal hygiene and health maintenance. The most favorable opportunity for reaching an employee with health education and counselling arises when he visits a health facility.
   Health education appropriately goes hand in hand with safety education. The occupational health and safety personnel, therefore, should work cooperatively with supervisory personnel in imparting appropriate health and safety information to employees. Health and safety education should encourage habits of cleanliness, orderliness and safety, and teach safe work practices, the use and maintenance of available protective clothing and equipment, and the use of available health services and facilities. Experience has shown that health education is most effective when the employer demonstrates his sincere and continuing interest in the health of his employees and when employees are encouraged to participate in the planning and conduct of health education activities.

ORGANIZATION AND STAFFING

In order to provide a satisfactory occupational health program, it is essential that a qualified doctor of medicine be engaged to direct the program. The needs of a specific program will determine the amount of time required of this physician. Training and experience in occupational medicine are desirable. The medical director should have a major role in the development, interpretation and implementation of medical policy. He should administer the occupational health program and be directly responsible to a designated official at the policy making level of management.

Physicians participating in the program:

1. Should maintain high standards of professional service and conduct for the benefit of employee and employer alike;
2. Should cooperate and maintain proper liaison with other physicians in the community and with the county medical society;
3. Should not use their occupational health affiliations improperly as a means of gaining or enlarging a private practice among employees; and
4. Should be engaged and compensated in accordance with the Principles of Medical Ethics of the American Medical Association (Special Edition of J. A. M. A., June 7, 1958).

The occupational health program should be tailored to each employee group according to its needs. These needs are determined by such factors as the number of employees in the group, the nature and extent of the hazards to which they are exposed, and the availability of community medical services. The personnel required in an occupational health program may include, in addition to physicians and nurses, persons skilled in various technological procedures of environmental appraisal and control, laboratory technicians, other specialized personnel and clerical help. The amount of time required of such personnel will depend upon the needs of the employee group to be served. The organizational relationships within the group, while varying with circumstances, should be such as to promote maximum collaboration and cooperation.

Nurses in occupational health programs should be graduates of accredited schools of nursing, registered and legally qualified to practice nursing where employed. Training and experience in occupational health are desirable. The nurse's professional duties should be clearly defined in writing by the physician.

In establishments which do not have a nurse, there should be one or more employees qualified in first aid available throughout the working hours. It is desirable, of course, in all employee groups to have a substantial proportion of the employees trained in first aid in the event of emergencies.

Cooperation among physicians, industrial hygienists, nurses, technicians and other occupational health personnel and management personnel responsible for the employment, safety and well-being of employees is essential. Occupational health personnel should cooperate also with voluntary and official community agencies providing health, safety, employment and welfare services.

FACILITIES

The extent of the facilities, including equipment, will depend upon the needs of the employees and the scope of the occupational health program. The facilities may be available at the place of employment or elsewhere in the community. Facilities when provided on the premises:

1. Should be located in a quiet area readily accessible to employees and to transportation;
2. Should be sufficiently spacious, well lighted, ventilated, and heated;
3. Should include waiting, consultation, examining, and treatment rooms, and toilet facilities, to insure adequate privacy and comfort;
4. Should have appropriate medical, laboratory, and other equipment; and
5. May include a rest or recovery room, dressing rooms, and facilities for laboratory and radiological examinations.

SUMMARY

This statement provides only a broad outline of the scope, objectives and functions of occupational health programs. More detailed information can be found in reference works on various aspects of occupational health and through consultation with persons whose professional training and experience have qualified them as specialists in this field. Guidance concerning the development and operation of occupational health programs also may be obtained from county and state medical societies and from the Council on Occupational Health of the American Medical Association.

The goal of occupational health programs in assuring the health of people who work is based on the recognition that the fullest development of our material resources is dependent upon a correspondent development of our human resources.

addition, most of these laws require employers to provide medical care for employees with occupational disease. These and other laws have given employers a greater incentive, as well as an obligation, to maintain safe and healthful working environments. The problems associated with the increasingly complex technology of industry, with ever new, potentially hazardous, physical and chemical agents, have served as an important stimulus to the development of occupational health programs. From these developments the earlier concept of curative occupational medicine has been broadened to include and emphasize prevention and health maintenance, and there has gradually emerged the type of occupational health program described in this statement.

Organized medicine should exercise leadership in improving occupational health programs and in providing adequate occupational health services to all employees, including those in small establishments. The medical profession has a responsibility to bring to the attention of industrial management and labor the values of occupational health services. In assuming this responsibility, the profession should recognize that the considerations and recommendations contained in this statement should not be viewed as being limited to full-time, salaried physicians. They should serve to attract and guide physicians in private practice in rendering part-time or consultant services. It is specifically in the provision of occupational health services to small plants that physicians in private practice can make their greatest contribution. The county medical society should be prepared to help employers locate physicians willing and qualified to direct and serve occupational health programs.

GENERAL CONSIDERATIONS

Health maintenance is primarily the responsibility of the individual. However, the employer has an obligation to provide a safe work environment for his employees and he has a valid interest in the prevention of loss of work time and of work efficiency resulting from his employees' ill health. Definitive diagnosis and therapy of nonoccupational injury and illness are not responsibilities of the employer, but he may provide certain preventive health measures in a given situation where the employee, the employer and the community stand to benefit.

There are two types of health programs for those who work. The one that is dealt with in this statement is the occupational health program that deals with the health of employees in relation to their work and is largely preventive. The other type is a medical care program for nonoccupational illnesses and injuries. These two types of programs differ in such respects as methods of financing and amounts and kinds of services. Failure on the part of employers, employees and physicians properly to distinguish between these two types of programs sometimes gives rise to misunderstandings and problems, particularly in those few situations in which the same professional personnel serves both programs.

OBJECTIVES

The objectives of an occupational health program are:

1. To protect employees against health hazards in their work environment;
2. To facilitate the placement and insure the suitability of individuals according to their physical capacities, mental abilities and emotional make-up in work which they can perform with an acceptable degree of efficiency and without endangering their own health and safety or that of their fellow employees;
3. To assure adequate medical care and rehabilitation of the occupationally ill and injured; and
4. To encourage personal health maintenance.

The achievement of these objectives benefits both employees and employers by improving employee health, morale and productivity.

ACTIVITIES

In order to attain these objectives the following activities are essential:

1. Maintenance of a healthful work environment.
   This requires that personnel skilled in industrial hygiene perform periodic inspections of the premises, including all facilities used by employees, and evaluate the work environment in order to detect and appraise health hazards, mental as well as physical. Such inspections and appraisals, together with the knowledge of processes and materials used, provide current information on health aspects of the work environment. This information will serve as the basis for appropriate recommendations to management for preventive and corrective measures.
2. Health examinations.
   a. Preplacement examinations.
      These examinations serve to determine the health status of the individual in order to aid in suitable placement. Such examinations should include:
      (1) Personal and family medical history;
      (2) Occupational history; and
      (3) Physical examination, including appropriate laboratory procedures.
   b. Periodic examinations.
      These health evaluations are similar to preplacement examinations and are carried out at appropriate intervals to determine whether the employee's health is compatible with his job assignment and to detect any evidence of ill health which might be attributable to his employment. Certain employees and groups may require examinations more frequently than others and additional procedures and tests, depending on their age, their physical condition, and the nature of their work.

All health examinations must be conducted by a physician with such assistance as he requires. The examination may be made in any properly equipped medical facility, at the place of work or elsewhere. However, to qualify as an appropriate part of the occupational health program, the examination must evaluate the health status of the employee in relation to his work.

The individual to be examined should be informed by appropriate means of the purpose and value of the examination. The physician should discuss the findings of the examination with the individual, explaining to him the importance of further medical attention for any significant health defects found.

Unrealistic and needlessly stringent standards of physical fitness for employment defeat the purpose of health examinations and of maximum utilization of the available work force.

3. Diagnosis and treatment.
   a. Occupational injury and disease.
      Diagnosis and treatment in occupational injury and disease cases should be prompt and should be directed toward rehabilitation. Workmen's compensation laws and policies of medical societies usually govern the provision of medical services for such cases. Further guidance is offered in the AMA statement "Medical Relations in Workmen's Compensation," in item 4 of the section on "Statutory Provisions." This appeared in the 1955 annual report of the Council on Industrial Health (J. A. M. A. 159:906-910 [Oct. 29] 1955). The statement was adopted, slightly changed, by the House of Delegates (J. A. M. A. 159:1648-1649 [Dec. 24] 1955). Reprints may be obtained from the Council on Occupational Health. Item 4 appears as paragraph (d) on page 4 of the reprint.
   b. Nonoccupational injury and illness.
      Diagnosis and treatment in nonoccupational injury and illness cases are not responsibilities of an occupational health program with the limited exceptions noted below:
      (1) In an emergency the employee should be given the attention required to prevent loss of life or

Income in excess of costs, expenses, and other charges		326,265
Fund balance at beginning of year		6,090,638
Add:		
Decrease in reserve for liability on *uncompleted contracts*—rehabilitation of buildings		1,770,000
Decrease in reserve for funding of depreciation of property, building, and equipment		201,238
		8,388,141
Less:		
Provision for reserve for replacement of building and equipment above original cost	3,347,605	
Increase in net investment in property, building, and equipment	1,945,084	
Demolition write off	206,407	
		5,499,096
Fund balance at end of year		$ 2,889,045

See accompanying notes to financial statements.

AMERICAN MEDICAL ASSOCIATION
Notes to Financial Statements
December 31, 1959

(1) Because of the various changes in expense classifications effective January 1, 1959, the 1959 expense factors are not wholly comparable to the 1958 factors and, accordingly, the 1958 figures have been omitted from this report.

(2) During the year 1959 the rehabilitation of the general office building was substantially completed. Therefore, the costs incurred to date and the estimated costs to be incurred subsequent to December 31, 1959 were recorded on the books of the Association as at December 31, 1959, as completed construction in the building account. The estimated costs to be paid subsequent to December 31, 1959, aggregating $353,113, were recorded as contracts payable.

(3) During the rehabilitation program certain portions of the building were removed or razed. The costs applicable thereto amounted to $452,602 with an accumulated allowance for depreciation of $246,195. Accordingly, the building and the allowance for depreciation accounts were relieved of such amounts with a corresponding charge of $206,407 made to the fund balance, as shown in Exhibit B.

(4) A reserve was provided at December 31, 1959 for the replacement of the building and equipment based upon the excess of the appraised insurable value at December 31, 1959 over the net book value of the depreciable fixed assets of the Association.

GOVERNMENT SERVICES

AIR FORCE

Course in Aerospace Medicine Completed.—Thirteen senior medical officers from 11 allied air forces completed the first class of the Advanced Course in Aerospace Medicine for Allied Officers at the U. S. A. F. School of Aviation Medicine in March. These flight surgeons will return to Brazil, Japan, Korea, Norway, the Philippines, Portugal, Spain, Taiwan, Thailand, Turkey, and Venezuela and serve as consultants, investigators, teachers, and directors of programs in this field with their respective air forces. These doctors, all graduates of the school's primary course in aviation medicine, read, write, and speak English fluently and have practiced aviation medicine for at least one year.

VETERANS ADMINISTRATION

The Aging Veteran.—The Veterans Administration is strengthening its medical services for the aging and chronically ill, and is completing a comprehensive study of problems of aging veterans. Day-care centers are being provided for medical patients, community home care plans for patients and planned living programs for domiciliary residents are being developed, and follow-up volunteer services for patients after leaving the hospital are being extended. Three geriatric clinics have been established and rehabilitation services are being extended from the clinics into the homes of veterans with service-connected disabilities.

PUBLIC HEALTH SERVICE

Nursing Home Services.—A nursing home services section was established within the chronic disease program of the division of special health services in the bureau of state services. This section provides information on matters relating to clinical services, administrative management, and licensing of nursing homes and homes for the aged. The unit will conduct studies and analyze needs relating primarily to services given in such facilities and develop guides for their operation. It will also develop guides relating to state licensure laws, rules, and regulations pertaining to nursing homes and homes for the aged. Dr. Bruce Underwood is chief of the section.

FOOD AND DRUG ADMINISTRATION

Orange Juice.—The standards for commercially packed orange juice, including undiluted and concentrated juices, now require that labels bear information that will identify and describe the kind of product being offered. For example, regular orange juice, which has been heated to destroy enzymes and micro-organisms to make it keep longer, must be labeled "pasteurized orange juice." Any orange juice product made entirely or partially from concentrate must bear a statement of that fact, such as "orange juice from concentrate" or "prepared in part from concentrated orange juice." If the product is prepared in part from water extract of orange pulp, the label of a concentrate must carry a statement such as "prepared in part from water extract of orange pulp."

Products sold as concentrates to which the consumer adds water, and juices already prepared from concentrates, are both required by the standards to have a specified proportion of sugar to acid. The amount of water is restricted. The standards allow natural sugars or orange juice concentrates to be added as optional ingredients to "sweetened" orange juice, but a sweetener may not be used in such a way as to replace any part of the orange juice solids required to be in an unsweetened product. The addition of regular juice to flavor a product sold as a concentrate is permitted. The standards do not permit the use of artificial sweeteners or chemical preservatives.

Annual and Clinical Meetings

The following places and dates have previously been approved for annual and clinical meetings of the Association:

Annual Meetings:

1961—New York, June 26-30
1962—Chicago, June 11-15

Clinical Meetings:

1960—Washington, D. C., November 28-December 1
1961—Denver, November 27-30
1962—Los Angeles, November 25-29

Respectfully submitted,

Leonard W. Larson, M.D., Chairman
Julian P. Price, M.D., Vice Chairman
Hugh H. Hussey, Jr., M.D., Secretary
James Z. Appel, M.D.
George M. Fister, M.D.
Percy E. Hopkins, M.D.
Raymond M. McKeown, M.D.
Cleon A. Nafe, M.D.
Rufus B. Robins, M.D.
Louis M. Orr, M.D.
E. Vincent Askey, M.D.

ACCOUNTANTS' REPORT

The Board of Trustees
American Medical Association:

We have examined the statement of assets, liabilities, and fund balance of American Medical Association as of December 31, 1959 and the related statement of income and fund balance for the year then ended. Our examination was made in accordance with generally accepted auditing standards, and accordingly included such tests of the accounting records and such other auditing procedures as we considered necessary in the circumstances.

In our opinion, the accompanying statements of assets, liabilities and fund balance and income and fund balance present *fairly* the financial position of American Medical Association at December 31, 1959 and results of its operations for the year then ended, in conformity with generally accepted accounting principles applied on a basis consistent with that of the preceding year.

Peat, Marwick, Mitchell & Co.

Chicago, Illinois
February 26, 1960

Exhibit A

AMERICAN MEDICAL ASSOCIATION

Statement of Assets, Liabilities and Fund Balance
December 31, 1959 with comparative figures for 1958

Assets	1959	1958
Cash	$ 125,063	179,418
Accounts receivable:		
Advertising	573,564	656,737
Directory report service	14,668	9,371
Other	167,135	92,503
	755,367	758,611
Interest accrued on investments	47,818	55,693
Inventories	357,173	362,199
Prepaid expenses, deposits and advances:		
Deposits and advances	114,304	85,762
Insurance and other prepayments	53,480	25,978
	167,784	111,740
Investments, at cost, of which $974,275 and $3,347,605 at December 31, 1959, are allocated to funded reserves for depreciation and fixed asset replacement, respectively (security values based on market quotations—1959, $9,474,997; 1958, $10,874,267—other investments based on cost:		
United States Government securities	6,425,969	7,863,056
Industrial bonds	5,000	5,000
Common stocks	2,593,243	2,152,913
Other investments	509,857	320,172
	9,534,069	10,341,141
American Medical Association Research Fund:		
United States Government securities, at cost (value based on market quotations—1959, $1,373,363; 1958, $1,422,666)	1,485,404	1,486,279
Cash	15,171	14,296
	1,500,575	1,500,575
Property, building, and equipment, at cost (notes 2 and 3)	5,282,443	3,538,577
Less allowance for depreciation (note 2)	974,275	1,175,513
	4,308,168	2,363,064
	$16,796,017	15,672,461

See accompanying notes to financial statements.

Liabilities and Fund Balance	1959	1958
Accounts payable and accrued expenses:		
Accounts payable	$ 1,088,805	650,032
Accrued payroll	49,241	36,975
Accrued taxes	108,838	91,172
Employees' withholding taxes	65,948	55,536
Contracts payable (note 2)	353,113	...
	1,665,945	833,715
Deferred credits:		
Unexpired subscriptions to publications	2,062,256	1,918,056
Other, including dues received in advance	48,148	20,850
	2,110,404	1,938,906
Net investment in property, building, and equipment	4,308,168	2,363,064
Reserves for:		
American Medical Association Research Fund	1,500,575	1,500,575
Replacement of building and equipment *above original cost*	3,347,605	...
Funding of depreciation of property, building, and equipment	974,275	1,175,513
Liability on uncompleted contracts—rehabilitation of buildings	...	1,770,000
	5,822,455	4,446,088
Fund balance	2,889,045	6,090,688
	$16,796,017	15,672,461

Exhibit B

AMERICAN MEDICAL ASSOCIATION

Statement of Income and Fund Balance
Year ended December 31, 1959

Income:		
Membership dues and subscriptions to periodical publications		$ 5,790,195
Advertising		8,083,972
Income from investments		436,731
Directory report service		388,620
Annual and interim meetings		414,192
Other income		154,311
		15,268,021
Costs, expenses, and other charges:		
Board of trustees	$ 816,328	
Executive vice-president	942,883	
Scientific activities division	1,070,134	
[illegible] division	880,359	
[illegible]	570,736	
[illegible]	1,232,035	
[illegible]	183,492	
Washington office	118,292	
Law division	186,069	
Business division	8,941,431	14,941,759

and hearing examinations along with medical, social, and nursing services, the following remain to be held:

April 19–Belleville, St. Elizabeth's Hospital.
April 19–Danville, Lake View Hospital.
April 20–Chicago Heights (general), St. James Hospital.
April 21–Bloomginton, a. m. (general), p. m. (cerebral palsy), St. Joseph's Hospital.
April 21–Elmhurst (cardiac) Memorial Hospital of DuPage County.
April 21–Rockford, Rockford Memorial Hospital.
April 26–Effingham (rheumatic fever), St. Anthony Hospital.
April 26–Peoria, Children's Hospital.
April 27–Carrollton, First Baptist Church.
April 27–Elgin, Sherman Hospital.
April 28–Mt. Vernon, Masonic Temple.

Any private physician may refer to or bring to a convenient clinic any child for whom he may want examination or consultative services.

Chicago

Lecture on Child Psychiatry.—The Chicago Council of Child Psychiatry is sponsoring a lecture and movie demonstration on Monday, April 25, in the auditorium of the Psychosomatic and Psychiatric Institute of Michael Reese Hospital, 2945 S. Ellis Ave., at 8 p. m. Dr. Robert C. Prall, of the Eastern Pennsylvania Psychiatric Institute, Philadelphia, will present "Motility Disturbances in Childhood Psychosis." For information, write Dr. Maurice J. Rosenthal, Secretary, Chicago Council of Child Psychiatry, 737 N. Michigan Ave., Chicago 11.

Camp for Diabetic Children.—The summer camp for diabetic children will be conducted for the 12th year under the auspices of the Chicago Diabetes Association July 17-Aug. 7 at Holiday Home, Lake Geneva, Wis. Boys and girls 8 through 14 years of age are eligible. Rates are arranged to fit individual circumstances. The camp will be staffed by resident physicians, a nurse, two dietitians, and a laboratory technician, in addition to the regular counseling and domestic staff. Applications may be obtained from the Chicago Diabetes Association, 5 S. Wabash Ave., Chicago 3.

Dustfall in Chicago.—The Armour Research Foundation of the Illinois Institute of Technology reported the chemical analysis of dustfall data for the City of Chicago for the month of February. The highest total dustfall in tons per square mile for a month of 30 days at the 25 stations was that of 123.1 tons at a southside station. The lowest total dustfall of 19.9 tons per square mile per 30-day month was at a westside station. Average total dustfall for the month for the loop area was 112.5 tons, which included 81.4 tons of water insoluble constituents and 31.1 tons of water soluble constituents. Average total dustfall for the month for the city including the loop was 55.4 tons per square mile, including 28.8 total water insoluble constituents and 26.6 total water soluble constituents.

Dr. Andelman Named Health Commissioner.—The appointment of Dr. Samuel L. Andelman as commissioner of the Board of Health for the City of Chicago was announced March 23. Dr. Herman N. Bundesen, who has been serving as administrator of the Chicago Board of Health, will continue in his position as president of the board but will relinquish his function as department administrator. Dr. Andelman has been assistant commissioner of health since September, 1956. A native of Chicago, he was graduated from the University of Illinois Medical School. From 1941 to 1945, he held a rank of captain in the U. S. Public Health Service. From 1945 to 1952, he was health officer of Harian County, Kentucky, and then served as regional health officer for the Illinois Department of Health, with headquarters at Carbondale, from 1952 to 1956. Dr. Bundesen began work for the health department in 1914.

KANSAS

Annual Clendening Lecture.—Dr. John B. de C. M. Saunders, dean, University of California School of Medicine, San Francisco, gave the annual Clendening Lecture at the University of Kansas School of Medicine March 21. His subject was "The Transition from Ancient Egyptian to Greek Medicine." The lecture series was established in 1949 by the widow of the late Dr. Logan Clendening of the University of Kansas, who was a faculty member for many years prior to his death in 1946.

NEBRASKA

Dr. Heaney Receives Faculty Award.—Dr. Robert P. Heaney, assistant professor of medicine, Creighton University School of Medicine, Omaha, received the Lederle Medical Faculty Award in recognition of his ability as a teacher and scientific investigator. Dr. Richard L. Egan, dean of the school, said the three-year award is valued at $6,199. Dr. Heaney graduated from the Creighton School of Medicine in 1951. Previously, he taught and carried on research at Oklahoma School of Medicine, Oklahoma Medical Research Foundation, and George Washington University School of Medicine, and was a research member of the National Institute of Arthritis and Metabolic Diseases.

NEW YORK

Fellowship Available for Research or Study.—The Glorney-Raisbeck Fellowship in the Medical Sciences will be awarded by the Committee on Medical Education, New York Academy of Medicine, for one year of research or study in any field of medicine or its allied sciences. The initial award will be for the academic year beginning July 1, 1961. Under circumstances deemed appropriate by the committee, the fellowship is renewable on a year-to-year basis for two additional years. The fellowship, which carries a stipend of $5,000, is open only to

MEDICAL NEWS

ALABAMA

Clinical Meeting in Tuskegee.—The John A. Andrew Clinical Society, in conjunction with the John A. Andrew Memorial Hospital, will meet April 24-29 at the hospital's Tuskegee Institute. The program includes lectures, clinical case presentations, and symposiums, and among the participants will be Dr. F. J. L. Blasingame, Executive Vice-President, American Medical Association. For information, write Dr. Eugene H. Dibble Jr., Secretary, John A. Andrew Clinical Society, Tuskegee Institute, Alabama.

Annual Meeting in Mobile.—The Medical Association of the State of Alabama will hold its annual session at the Admiral Semmes Hotel, Mobile, April 21-23 under the presidency of Dr. William R. Carter, Repton. Dr. Frank H. Krusen, committee of rehabilitation, American Medical Association, Washington, D. C., will present "Rehabilitation Adds Life to Years" the afternoon of April 21, and Dr. F. J. L. Blasingame, Executive Vice-President of the A. M. A., Chicago, will give "Leadership and Legislation" the morning of April 22. The program includes the following papers:

The Surgeon Takes a Look at Traumatic Injuries of the Face, Dr. Arthur N. Owens, New Orleans.
The Use and Abuse of Hormones in Children, Dr. Alvin B. Hayles, Rochester, Minn.
The Jerome Cochran Lecture: Changing Concepts in the Treatment of Cancer of the Cervix, Dr. Joe V. Meigs, Boston.
Polycystic Ovary Syndrome, Dr. Robert B. Greenblatt, Augusta, Ga.
Radiation: Physician and Patient, Dr. David S. Carroll, Memphis.

Seven specialty groups will meet during the annual session. Technical exhibits are planned. A golf tournament will be held April 20, and the president's ball is planned for April 22, 8 p. m. For information, write Mr. W. A. Dozier Jr., 19 S. Jackson St., Montgomery, Ala., Executive Secretary.

ARKANSAS

State Session in Pine Bluff.—The 84th annual session of the Arkansas Medical Society will be held April 17-20 at the Pines Hotel, Pine Bluff. Dr. James M. Kolb, Clarksville, will present the president's address at the opening general session, the morning of April 18. Participants in the scientific program will include the following out-of-state speakers:

Drs. Albert B. Hagedorn, Rochester, Minn.; Harvey Blank, Miami; Denton A. Cooley, Houston, Texas; Carleton B. Chapman, Dallas; Charles R. Stephen, Durham, N. C.; Harry D. Morris, New Orleans; George M. Haik, New Orleans; Robert Lich Jr., Louisville, Ky.; Blair E. Batson, Jackson, Miss.; Isadore Meschan, Winston-Salem, N. C.; John R. Snavely, Jackson, Miss.

Six specialty groups will meet April 19 and the annual banquet will be held that evening. Scientific and commercial exhibits are planned. Entertainment includes a golf tournament. For information, write Mr. Paul C. Schaefer, 218 Kelly Bldg., Ft. Smith, Ark., Executive Secretary.

CONNECTICUT

State Meeting in Hamden.—On April 26-28, the Connecticut State Medical Society will hold its 168th annual meeting at the Hamden High School, Hamden, under the presidency of Dr. Ellwood C. Weise Sr., Bridgeport, who will open the meeting the morning of April 27. The following papers will be presented by out-of-state speakers:

New Chemotherapeutic Agents for Malignancy, Dr. James F. Holland, Buffalo, N. Y.
The Treatment and Outlook for Parkinson's Disease, Dr. Lewis J. Doshay, New York City.
Diet in Coronary Disease, Dr. Herbert Pollack, New York City.
Biochemical Genetics, Dr. James B. Sidbury Jr., Baltimore.
Current Knowledge of Viral Hepatitis, Dr. W. Paul Havens Jr., Philadelphia.
Treatment of Congenital Lesions of the Gastro-Intestinal Tract, Dr. Thomas V. Santulli, New York City.
Stress Incontinence, Diagnosis and Treatment, Dr. C. Paul Hodgkinson, Detroit.
Surgical Consideration in Treatment of Cerebral Arterial Insufficiency, Dr. E. Stanley Crawford, Houston, Texas.

Dr. Louis H. Bauer, New York City, Secretary General, World Medical Association, will present "Blue Shield and the Medical Profession" at noon on April 27. A panel discussion, "Urological Problems in General and Gynecologic Surgery," and a film, "Facts About Fall-Out," are planned. Specialty groups will meet April 27 and 28. Forty-nine technical exhibits will be on display. The annual dinner of the society will be held April 27, 7 p. m. For information, write Dr. William R. Richards, 160 St. Ronan St., New Haven, Conn., Secretary.

ILLINOIS

Clinics for Crippled Children.—Of the 23 clinics for physically handicapped children scheduled for April (18 general clinics by the University of Illinois, Division of Services for Crippled Children) to provide diagnostic orthopedic, pediatric, speech,

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Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

Nuclear Reactor Radiology in Clinical Medicine, Dr. Lee E. Farr, Upton, N. Y.
Lessons from Rare Diseases and Rare Lesions, Dr. William B. Bean, Iowa City.
Changing Concepts Underlying the Surgical Approach to Occlusive Disease of the Lower Extremities, Dr. Michael E. DeBakey, Houston, Texas.
A Patient's Pilgrimage Through Medical History, Dr. Bean.
Surgical Considerations of Aneurysms of the Abdominal and Thoracic Aorta, Dr. DeBakey.
Technology, Basic Science and Clinical Medicine in an Atomic Age, Dr. Farr.
Surgery of Cerebrovascular Insufficiency, Dr. DeBakey.
Educational Concepts in Nuclear Medicine, Present and Future, Dr. Farr.
The Patient with Pain in the Chest, Dr. Bean.

The Sigma Xi Lecture, "Sex Reversal in Animals and Man," will be given by Emil Witschi, Ph.D., Iowa City, the afternoon of April 21. Founded in 1913, the alumni association includes groups of the Willamette University department of medicine. The program is acceptable for 14 hours category II credit by the American Academy of General Practice. For information, write Dr. Arthur W. Sullivan, Secretary, Alumni Association, University of Oregon Medical School, Portland 1, Ore.

SOUTH CAROLINA

Annual Meeting in Myrtle Beach.—The South Carolina Medical Association will meet May 18-19 at Myrtle Beach. A symposium on glaucoma May 18 will be moderated by Dr. Julius H. Stokes, Florence. Panel discussions will include cardiovascular disease, perinatal problems, hormone and chemotherapy of cancer, and geriatrics. The following papers are scheduled:

Griseofulvin, Dr. Kathleen A. Riley, Charleston.
Aortic Valvular Disease, Dr. William H. Mueller Jr., Charlottesville, Va.
Pregnancy Following Operative Delivery, Dr. Robert A. Cosgrove, Jersey City, N. J.
Obstetrician's Responsibility in the Prevention of Neurologic Disease in Children, Dr. George W. Anderson, Baltimore.
Acute Management of the Severely Burned Patient, Dr. Edward T. Krementz, New Orleans.
Leap Year Gerontology and Geriatrics, Dr. Arthur C. McCarty, Louisville, Ky.
The Natural History of Arteriosclerosis Obliterans, Dr. Edgar V. Allen, Rochester, Minn.
Basic Psycho-Therapy, Dr. Kenneth E. Appel, Philadelphia.
Portal Hypertension and Bleeding Esophageal Varices, Dr. R. Randolph Bradham, Charleston.

Scientific and commercial exhibits are planned. The presidential address will be given by Dr. William Weston Jr., Columbia, the afternoon of May 18. For information, write Mr. M. L. Meadors, 309 W. Evans St., Florence, S. C., Executive Secretary.

GENERAL

General Practice Group Joins Health Council.—The American Academy of General Practice is the latest addition to the membership of the National Health Council. The election of the academy brings the council membership to an all-time high of 71. The National Health Council, established in 1921, brings together the principal voluntary, professional, and governmental health agencies and selected business and civic groups concerned with health improvement. The council's address is 1790 Broadway, New York 19.

Annual Session on School Health.—The second annual Pre-Convention School Health Session on School Health, jointly sponsored by the American Medical Association and the American School Health Association, will be held on Sunday June 12, 7:30 p. m., in the Medallion Room of the Carillon Hotel, Miami Beach, Fla. A symposium will be presented by authorities in school health from several professional fields and there will be an opportunity for discussion from the floor. Physicians attending the A. M. A. meeting who are interested in the health of school-age children are cordially invited.

Society News.—On March 17, Dr. James E. Perkins, of New York City, became president of the National Health Council. Dr. James H. Sterner, Rochester, N. Y., was named president-elect to succeed Dr. Perkins in 1961. The council, founded in 1920, has as members 71 national voluntary health agencies, professional societies, and public service organizations.——Officers of the Western Society for Clinical Research are as follows: president, Dr. Charles G. Craddock Jr., Los Angeles; vice-president, Dr. George E. Cartwright, Salt Lake City; and secretary-treasurer, Dr. William N. Valentine, University of California Medical Center, Department of Medicine, Los Angeles 24.

Camp for Epileptic Children.—The second annual summer camp program for children with epilepsy is scheduled to get underway June 6 at the National Children's Rehabilitation Center, Leesburg, Va. Applications for admission are being accepted, according to Charles Kram, Ph.D., director. The center is a nonprofit facility supported by the Federal Association for Epilepsy in Washington, D. C. Children between the ages of 7 and 12, from all parts of the country, are eligible for admission. Children will be admitted for periods ranging from two weeks up to the duration of the summer. Swimming, overnight hikes, camp craft, dancing, and art are among the activities planned. Fees for the camp program, like those for the regular year-round program, are based on each family's financial situation. For information, write the Federal Association for Epilepsy, Inc., 1729 F St., N. W., Washington 6, D. C.

Meeting on Sports Medicine.—The 1960 annual meeting of the American College of Sports Medicine will be held April 22-24 at the Saxony Hotel, Miami Beach, Fla. Dr. Albert S. Hyman, New York holders of the M.D. degree who have "demonstrated potential for productivity in research and teaching." In general, preference will be given to physicians from the Greater New York area. A candidate should be prepared to give assurance that he will have an institutional appointment which will enable him to carry out the objectives of his program of research or study. Such institutions will be encouraged to supplement the fellowship stipend. Candidates also should be prepared to be interviewed by the committee (out-of-town candidates at their own expense). Deadline for receipt of applications is Sept. 1, 1960. Request for application forms and information should be addressed to Dr. Aims C. McGuinness, Executive Secretary, Committee on Medical Education, The New York Academy of Medicine, 2 E. 103 St., New York 29.

New York City

Dr. Kornberg to Lecture.—The eighth annual Emanuel B. Schoenbach Memorial Lecture will be delivered in the Solarium of the Kronish Pavilion of the Maimonides Hospital of Brooklyn on Friday, April 29, at 5 p. m. The speaker will be Dr. Arthur Kornberg, director, department of biochemistry, Stanford University School of Medicine, Palo Alto, Calif., and Nobel Laureate in Medicine. Dr. Kornberg's talk will be "The Chemical Basis of Heredity."

Personal.—Dr. Gordon Ross Hennigar Jr., professor of pathology, has been made acting chairman, department of pathology, State University of New York–Downstate Medical Center, and acting director of the Institute of Pathology, Kings County Hospital, during the sabbatical leave of Dr. Patrick J. Fitzgerald, Brooklyn, chairman, who is at the department of biochemistry, Oxford University, England. Dr. Stanley M. Aronson, Brooklyn, professor of pathology, has been appointed associate director of the Institute of Pathology.——Dr. Morton I. Berson, who lectured before the Greater Miami Chapter of the Alpha Omega fraternity on Feb. 11 at the Mt. Sinai Hospital in Miami, Fla., on reconstructive and cosmetic plastic surgery, was awarded an honorary citation by the fraternity.

First Meeting of Internists.—The first annual assembly of the Society of Certified Internists of the County of New York was held March 14. The organization is a component of the New York State Society of Internal Medicine and of the American Society of Internal Medicine. Its principal aims are "to express the ideals of internal medicine and to foster its economic, social and scientific aspects and to advance public relations with governmental agencies, medical care insurance programs and the public in general." The following officers were elected to serve during the coming year: president, Dr. Seymour Lionel Halpern; vice-president, Dr. John James Mead, III; secretary, Dr. Jerome Gerendasy; treasurer, Dr. Richard S. Marton; and directors, Drs. Asa L. Lincoln, Alfonso A. Lombardi, Arthur M. Master, and Harry A. Solomon. The next meeting will be held May 9, 8:30 p. m., at the auditorium of the New York Medical College, Flower and Fifth Avenue Hospital. This will be an open meeting to which all board certified internists and members of the American College of Physicians are invited. The principal speaker will be Dr. Herbert Berger, Staten Island, president-elect, New York State Society of Internal Medicine, who will present "The Internist and Medical Care Insurance Programs."

OHIO

Exhibit on Arthritis and Rheumatism.—An exhibition for the general public, "The Mystery of Arthritis and Rheumatism," made possible by a grant from the Cleveland chapter of the Arthritis and Rheumatism Foundation and consisting of 40 units, was opened on March 19 at the Cleveland Health Museum. The exhibit deals with the history and scope of the diseases, the basic principles of treatment, including physical and occupational therapy, and the exploitation of the public through quack cures. Exhibit material will be available for loan after May 15. For information, write Dr. Bruno Gebhard, Director, Cleveland Health Museum, 8911 Euclid Ave., Cleveland 6.

Institute on Science in Law Enforcement.—Western Reserve University, Cleveland, will hold the seventh Institute on Science in Law Enforcement June 20-25, through the cooperation of the University's Law-Medicine Center and the coroner's office of Cuyahoga County. The institute will be comprised of 40 hours of lectures and demonstrations in criminal investigation and interrogation. The crimes of homicide and burglary will be studied, with attention given to the improved techniques used by law-enforcement officers. The lecturers and demonstrators include members of the Western Reserve University faculty, the professional staff of the coroner's office, experts from the Cleveland Police Department, and others. Tuition for the institute is $75. A program of social events is planned. For information, write Mr. Oliver Schroeder Jr., the Law-Medicine Center, 2145 Adelbert Rd., Cleveland 6.

OREGON

Alumni Meeting in Portland.—The Alumni Association of the University of Oregon Medical School will hold its 45th annual meeting Apr. 20-22, with scientific sessions held in the medical school auditorium. The program includes the following Sommer Memorial Lectures:

The Era of Rational Therapeutics, Dr. Keith J. R. Wightman, Toronto.
Beneficial Aspects of an Effective Environmental Health Program, Herbert M. Bosch, M. P. H., Minneapolis.
Failures and Psychiatric Illness in Medical Students, Dr. Aldwyn B. Stokes, Toronto, and Dr. John G. Dewan, Toronto.
The Physician's Responsibility in Medical Research, Dr. Ray F. Farquharson, Toronto.
Facts and Fallacies Concerning Urinary Excretion in Athletic and Physical Exertion, Dr. John H. Ebbs, Toronto.
Health Education Services Available Through the American Medical Association, Wallace Ann Wesley, H.S.D., Chicago.

At the banquet April 28, 7 p. m., Dr. Robert M. Janes, professor of surgery, emeritus, University of Toronto, will present "Africa Through a Camera." For information, write Dr. Norman S. Moore, Cornell University, Gannett Clinic, Ithaca, N. Y., Secretary-Treasurer.

CANADA

Annual Meeting in Banff.—The 93rd annual meeting of the Canadian Medical Association will be held June 13-17 in Banff, Alberta, with headquarters at the Banff Springs Hotel. Round-table conferences will be held each morning, June 15-17. Papers to be presented at the general sessions are as follows:

Secondary Operations on the Gallbladder and Bile Ducts, Dr. Richard B. Cattell, Boston.
Sex Chromatin, Sex Chromosomes and Sex Anomalies, Dr. Murray L. Barr, London, Ontario.
Blood Coagulation in Acute Renal Failure and Open Heart Surgery, Dr. Louis Lowenstein, Montreal.
Birth Injury and the Development of Neurological Lesions, Dr. Haddow M. Keith, Rochester, Minn.
An Improved Method for the Diagnosis of Solitary Pulmonary Nodules, Dr. L. Henry Garland, San Francisco.
Governments and Doctors, Dr. Edward R. C. Walker, Edinburgh, Scotland.
The Threat of the Modern Laboratory to the Art and Science of Medicine, Dr. Irwin M. Hilliard, Saskatoon.

The Osler Oration, "Sagacity and Science in the Practice of Medicine," will be given the morning of June 16 by Sir Francis Walshe, London, England. Section meetings are planned for June 15 and 16. For information, write Dr. Arthur D. Kelly, 150 St. George St., Toronto 5, Ontario, Canada, General Secretary.

FOREIGN

International Symposium on Hepatology.—On June 29-30, the second International Symposium on Hepatology, organized by the publication "Il Fegato," will be held at Chianciano-Terme, Siena, Italy. Prof. Luigi Condorelli, of Rome, is president of the executive committee. The symposium will consist of four meetings during which 16 papers will be read. There will be a scientific exhibit. Questions and comments will follow each paper. A pamphlet containing the summaries of the papers and of the communications will be published before the symposium, and a copy will be sent to all participants. The titles of the communications must be in the hands of the secretary of the symposium by April 30. By May 15, a brief summary, no more than 10 typewritten lines, of each communication must be sent. For information, write the Secretary of the Symposium Prof. C. Cervini, Via Nicolò Porpora 9, Rome, Italy.

Congress on Cell Biology in Paris.—The 10th congress of the International Society for Cell Biology is scheduled for Sept. 4-9 in Paris. The scientific program includes the following selected topics:

Nucleocytoplasmic Relationship in Cell Physiology.
Molecular Transport Across Membranes of Living Systems.
Membranes and Pinocytosis.
Comparison of Normal and Tumoral Cells in Tissue Culture.
Cellular Basis of Hormones Response.
The Application of Cinemicrography to the Study of the Cell.
Cell Degeneration and Cell Death.
Repopulation of Irradiated Tissues.

One main speaker and two general speakers will consider each topic. Short papers on various questions on cell biology but not related to the 12 selected topics are also planned. A film session is scheduled. For information, write the General Secretary, Prof. R. M. May, Laboratorie de Biologeanimale, rue Cuvier 12, Paris Ve, France.

CORRECTIONS

Intractable Trichomoniasis.—In the Question and Answer entitled "Intractable Trichomoniasis," in The Journal, Jan. 9, page 206, in line 16 of Dr. Moench's comment the word "appeared" should be changed to "disappeared."

Benzene Hydrochloride and Aplastic Anemia.—In the Question and Answer entitled "Benzene Hydrochloride and Aplastic Anemia," in The Journal, Nov. 14, 1959, page 1624, in lines 11, 20, and 30 of the answer the word "hexachloride" should be inserted instead of "hydrochloride."

EXAMINATIONS AND LICENSURE

EDUCATIONAL COUNCIL FOR FOREIGN MEDICAL GRADUATES, INC.

Educational Council for Foreign Medical Graduates: Stations around the world. Sept. 21, 1960. Exec. Director, Dr. Dean F. Smiley, 1710 Orrington Ave., Evanston, Ill.

NATIONAL BOARD OF MEDICAL EXAMINERS

National Board of Medical Examiners: Part I, Various Cities, June 21-22 and Sept. 7-8. Part II, Various Cities, April 26-27. Applications must be received at least six weeks before the date of the examination. Exec. Sec., Dr. John P. Hubbard, 133 South 36th St., Philadelphia.

City, president of the college, will open the scientific program the morning of April 23. At the third scientific session fireside chats are planned which include the following topics: Scientific Evaluation of the Effects of Exercise on Girls and Women, Cardiovascular Aspects of Sports Medicine, Orthopedic Aspects of Sports Medicine, and Physical Conditioning. At the annual college luncheon April 24, 12:30 p. m., Capt. Ashton Graybiel, director of research, United States Naval School of Aviation Medicine, Pensacola, Fla., will present "Physical Fitness for Space Travel." A symposium on space travel will follow the luncheon, at a joint session of the college and the American Academy of Physical Education. The annual business meeting of the college is planned for the morning of April 23. For information, write Grover W. Mueller, M.S., Parkway at 21st Street, Philadelphia 3, Secretary.

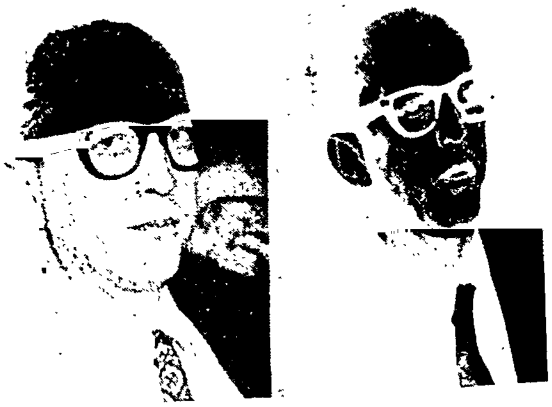
Psychoanalysis Meeting in Atlantic City.—The scientific session of the annual meeting of the Academy of Psychoanalysis will be held May 7-8 at the Hotel Claridge, Atlantic City, N. J., under the theme "The Nature of the Therapeutic Process." The following papers are scheduled:

An Experiential Theory of the Process of Psychoanalytic Therapy, Dr. William V. Silverberg, New York City.
The Nature of the Therapeutic Process, Dr. Norman A. Levy, Los Angeles.
Relief of Distress and Attitudinal Changes, Dr. Jerome D. Frank, Baltimore.
What Price Isolation? Dr. C. Knight Aldrich, Chicago.
The Intellectual Antecedents of Liberal Psychoanalysis, Dr. Milton Mazer, New York City.
General and Special Considerations of Acting Out, Dr. Salo Rosenbaum, New York City.
Minimal Brain Injury in Child Psychiatry, Dr. Margaret M. Lawrence, Pomona, N. Y.
Self-Alienation and Psychoanalytic Therapy, Dr. Frederick A. Weiss, New York City.

Dr. John A. P. Millet, New York City, will give the presidential address the afternoon of May 8. For information, write Dr. Joseph H. Merin, 125 E. 65 St., New York 21, Secretary.

Conference on Industrial Health.—Recent developments affecting the health of American workers will be under discussion when occupational health specialists convene for the 15th national Industrial Health Conference in Rochester, N. Y., April 25-30. General conference chairman is Mr. Herbert T. Walworth, director of industrial hygiene, Lumbermen's Mutual Casualty Company, Chicago. Conference emphasis will be placed on the provision of preventive medical services by industry and progress in the control of occupational health hazards. Papers will cover such subjects as heart disease in industry, cancer, radiation, mental health, industrial dentistry, noise, industrial nursing, air pollution, and toxicology of various substances related to industrial health. About 100 scientific exhibits will depict problems in worker health. The annual conference brings together five participating organizations, the Industrial Medical Association, American Association of Industrial Nurses, Inc., American Industrial Hygiene Association, American Association of Industrial Dentists, and American Conference of Governmental Industrial Hygienists, as well as representatives of industrial management, labor, and others concerned with industrial health. For information, write Dr. Matthew E. Fairbank, Kodak Park, Rochester 4, N. Y., Public Relations Chairman.

Wanted by F. B. I.—The Federal Bureau of Investigation is conducting an investigation to locate James Vincent La Duca, sought for violation of the Taft-Hartley Act. La Duca reportedly suffers from extreme sensitivity of the right carotid sinus, is highly nervous, moderately hypothyroid, and subject to fainting spells. He has reportedly been treated for Meniere's syndrome as well as a peptic ulcer. He has had a cholecystectomy and an appendectomy. La Duca is described as a white, 47-year-old male, 5 ft. 11 in. in height, weighing 174 lbs., with sandy brown or blond hair, receding in front. He has blue eyes, wears glasses, is of medium build, and reportedly has partial removable dentures, upper and lower, on both the right and left sides of mouth. Anyone having information concerning this man should contact the nearest office of the F. B. I., the telephone number of which may be found on the first page of any telephone directory.



James Vincent La Duca.

Meeting of College Health Association.—On April 27-30, the American College Health Association will meet at the Royal York Hotel, Toronto, Canada. Dr. Paul O. Greeley, Los Angeles, will present the president's address at the opening general session. Section meetings to be held concurrently April 28-29 will include clinical medicine, administration, mental health, nursing services, health education, environmental health and safety, and athletic medicine. Papers to be presented at the general sessions are as follows:

DEATHS

Apeldorn, Ernest Frederick II, Philadelphia; Hahnemann Medical College and Hospital of Philadelphia, 1904; died Feb. 10, aged 77.

Ballance, Charles, Atlanta, Ga.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1906; veteran of World War I; died in the Veterans Administration Hospital Feb. 2, aged 80, of cancer of the lung.

Barker, William Ermon Ⓜ Longview, Texas; Baylor University College of Medicine, Dallas, 1930: specialist certified by the American Board of Orthopaedic Surgery; member of the Clinical Orthopaedic Society and the American Academy of Orthopaedic Surgeons; interned at the Jefferson Davis Hospital in Houston; served a residency at the Long Island College Hospital in Brooklyn and the Jersey City Hospital in Jersey City; veteran of World War II; associated with Gregg Memorial and Markham Memorial hospitals; died Feb. 5, aged 53.

Bennardi, Anthony Maurice, Cleveland; University of Pennsylvania School of Medicine, Philadelphia, 1917; veteran of World War I; died Jan. 29, aged 69, of bilateral bronchopneumonia.

Bennett, William Aaron, Philadelphia; Hahnemann Medical College and Hospital of Philadelphia, 1909; also a graduate in pharmacy; died Feb. 6, aged 78.

Boston, Frank Erdman Ⓜ Lansdale, Pa.; Medico-Chirurgical College of Philadelphia, 1915; also a graduate in pharmacy; member of the American Fracture Association; fellow of the International College of Surgeons; veteran of World War I; associated with the North Penn Hospital; died in the Albert Einstein Medical Center, Philadelphia, Feb. 8, aged 68.

Brobst, Daniel Reuben, Parkersburg, W. Va.; Jefferson Medical College of Philadelphia, 1895; for many years practiced in Reading, Pa.; died in St. Joseph's Hospital Feb. 7, aged 87.

Burns, Jonathan Edward Ⓜ Charles Town, W. Va.; Johns Hopkins University School of Medicine, Baltimore, 1908; member of the American Urological Association; fellow of the American College of Surgeons; veteran of World War I; died in Phoenix, Ariz., Jan. 28, aged 77.

Burstan, J. Emerson, New York City; Jefferson Medical College of Philadelphia, 1916; died Jan. 6, aged 70, of acute pulmonary edema.

Busby, Lauren Fletcher, Santa Barbara, Calif.; University of Nebraska College of Medicine, Omaha, 1929; member of the American Trudeau Society; served as director of tuberculosis control and the crippled children's service, Santa Barbara County Health Department; formerly county health officer; died in the Cottage Hospital Jan. 30, aged 58, of thrombosis of the terminal aorta.

Callender, Eugene Frederick Ⓜ Chester, Conn.; Yale University School of Medicine, New Haven, 1912; served on the staffs of Waterbury (Conn.) Hospital, Middlesex Memorial Hospital in Middletown, and the Hartford (Conn.) Hospital, where he died Feb. 3, aged 70.

Carter, James Vincent, San Francisco; Jefferson Medical College of Philadelphia, 1951; interned at St. Joseph's Hospital and Dispensary in Pittsburgh; served a residency at St. Catherine's Hospital in Brooklyn and the Jennings Memorial Hospital in Detroit; for many years practiced in Cheyenne, Wyo.; from August, 1952, to January, 1954, an officer in the medical corps of the U. S. Naval Reserve; died Jan. 23, aged 33, of injuries received in a fall.

Ceraso, Thomas Ⓜ Vandergrift, Pa.; Jefferson Medical College of Philadelphia, 1923; veteran of World War I; member of the staffs of the Allegheny Hospital in Tarentum and the Citizens General Hospital in New Kensington; a director of the Kiski Valley National Bank; died Feb. 2, aged 60.

Clifford, Charles Henry Ⓜ Detroit; University of Toronto Faculty of Medicine, Toronto, Ont., Canada, 1924; member of the Industrial Medical Association; fellow of the International College of Surgeons and the American College of Surgeons; associated with the Detroit Memorial and Grace hospitals; died Feb. 1, aged 56, of acute coronary thrombosis.

Coates, George Morrison Ⓜ Philadelphia; born in Philadelphia March 24, 1874; University of Pennsylvania Department of Medicine, Philadelphia, 1897; professor emeritus of otolaryngology at his alma mater; for many years professor of otorhinology at the Graduate School of the University of Pennsylvania; veteran of the Spanish-American War and World War I; served as chairman of the Section on Otolaryngology of the American Medical Association; past-president and vice-president of the American Laryngological, Otological and Rhinological Society; for many years secretary of the American Laryngological Association, of which he was past-president; past-president of the Amer-

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Ⓜ Indicates Member of the American Medical Association.

BOARDS OF MEDICAL EXAMINERS

Alabama: *Examination.* Montgomery, June 21-23. Sec., Dr. D. G. Gill, State Office Bldg., Montgomery.

Alaska:° On application in Anchorage or Fairbanks. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

Arkansas:° *Examination and Reciprocity.* Little Rock, June 9-10 Sec., Dr. Joe Verser, Harrisburg.

California: *Written.* San Francisco, June 20-23; Los Angeles, Aug. 22-25 and Sacramento, Oct. 17-20. *Oral and Clinical.* Los Angeles, San Francisco, June 19; Los Angeles, Aug. 21, and Los Angeles, Nov. 29. *Oral for Reciprocity Applicants.* San Francisco, June 18; Los Angeles, Aug. 20 and Nov. 19. Sec., Dr. Louis E. Jones, Room 536, 1020 N Street, Sacramento.

Canal Zone: On Application. Acting Sec., Dr. B. K. Levin, Health Bureau, Balboa Heights.

Colorado:° *Examination.* Denver, June 14-15. Sec., Dr. John B. Farley, 1612 Tremont Place, Denver 2.

Delaware: *Examination and Endorsement.* Dover, June 12-14 and July 21. Sec., Dr. Joseph S. McDaniel, Professional Bldg., Dover.

District of Columbia:° *Examination.* Washington, June 13-14. Deputy Director, Mr. Paul Foley, Department of Occupations and Professions, 1740 Massachusetts Ave., N.W., Washington 6.

Florida:° *Examination.* Miami Beach, June 19-21. Sec., Dr. Homer L. Pearson, 901 N.W. 17th St., Miami 36.

Georgia: *Examination and Reciprocity.* Atlanta, June. Sec., Mr. Cecil L. Clifton, 224 State Capitol, Atlanta 3.

Guam: *Subject to Call.* Act Sec., Dr. F. L. Conklin, Agana.

Idaho: *Examination and Endorsement.* Boise, July 11-13. Exec. Sec., Mr. Armand L. Bird, 304 Sonna Bldg., Boise.

Indiana: *Examination.* Indianapolis, June 22-24. *Reciprocity.* Indianapolis, fourth Wednesday of each month. Ex. Sec., Miss Ruth V. Kirk, 538 K. of P. Bldg., Indianapolis.

Kentucky: *Examination.* Louisville, June 6-7. Sec., Dr. Russell E. Teague, 620 South Third St., Louisville 2.

Louisiana: *Examination and Reciprocity.* New Orleans, June 9-11. Sec., Dr. Edwin H. Lawson, 930 Hibernia Bank Bldg., New Orleans 12.

Maryland: *Examination.* Baltimore, June 15-18. Sec., Dr. Frank K. Morris, 1215 Cathedral St., Baltimore 1.

Michigan:° *Examination.* Ann Arbor and Detroit, June 6-8. Sec., Dr. E. C. Swanson, 118 Stevens T Mason Bldg., Lansing.

Mississippi: *Examination.* Jackson, June 20-21; *Reciprocity,* Jackson, June 16. Sec., Dr. A. L. Gray, Old Capitol, Jackson 13.

Missouri: *Examination.* St. Louis, May 27-28. Exec. Sec., Mr. John A. Hailey, State Capitol Bldg., P. O. Box 4, Jefferson City.

Nebraska:° *Examination.* Omaha, June 13-15, 1960. Dir., Bureau of Examining Boards, Room 1009, State Capitol Bldg., Lincoln 9.

Nevada: *Examination and Reciprocity.* Reno, June 8, Sept. 7 and Dec. 7. Sec., Dr. G. H. Ross, 112 North Curry St., Carson City.

New Mexico:° *Examination and Reciprocity.* Santa Fe, May 16-17. Sec., Dr. R. C. Derbyshire, 227 East Palace Ave., Santa Fe.

New York: *Examination.* Albany, Buffalo, New York City, Rochester and Syracuse, June 28-July 1. Sec., Dr. Stiles D. Ezell, 23 S. Pearl Street, Albany.

North Carolina: *Endorsement.* Raleigh, May 9. *Examination and Endorsement.* Raleigh, June 20-23. Sec., Dr. Joseph J. Combs, 716 Professional Bldg., Raleigh.

North Dakota: *Examination and Reciprocity.* Grand Forks, July 13-16. Sec., Dr. C. J. Glaspel, Grafton.

Ohio: *Reciprocity.* Columbus, June 17. *Examination.* Columbus, June 16-18. Sec., Dr. H. M. Platter, 21 West Broad St., Columbus 15.

Oklahoma:° *Examination and Endorsement.* Oklahoma City, May 31-June 1. Sec., Dr. E. F. Lester, 813 Braniff Bldg., Oklahoma City.

Oregon:° *Examination.* Portland, July. Exec. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland.

Pennsylvania: *Examination.* Philadelphia and Pittsburgh, July 5-7. Sec., Mrs. Margaret G. Steiner, Box 911, Harrisburg.

South Carolina: *Endorsement.* Myrtle Beach, May 17. *Examination.* Columbia, June 28-29. Sec., Dr. Harold E. Jervey, Jr., 1329 Blanding St., Columbia.

Texas:° *Examination and Reciprocity.* Fort Worth, June 20-22. Sec., Dr. M. H. Crabb, 1714 Medical Arts Bldg., Fort Worth 2.

Utah: *Examination.* Salt Lake City, July 6-8. Director, Mr. Frank E. Lees, 324 State Office Bldg., Salt Lake City 1.

Vermont: *Examination and Reciprocity.* Burlington, June 16-18. Sec., Dr. F. J. Lawliss, Richford.

Virgin Islands: *Examination.* Charlotte Amalie, St. Thomas, June 8-9. Sec., Dr. Benjamin A. Nath, Charlotte Amalie, St. Thomas.

Virginia: *Examination and Reciprocity.* Richmond, June 13-17. Address: Board of Medical Examiners, 631 First St. S.W., Roanoke.

West Virginia: *Examination and Reciprocity.* Charleston, *April 18. Sec.,* Dr. Newman H. Dyer, State Office Bldg. No. 3, Charleston 5.

Wyoming: *Examination and Reciprocity.* Cheyenne, June 6. Acting Sec., Dr. Carleton D. Anton, State Office Bldg., Cheyenne.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

Arkansas: *Examination.* Little Rock, April 21-22. Sec., Dr. A. W. Ford, Department of Education, Education Bldg., Little Rock.

District of Columbia: *Examination.* Washington, May 23-24. Deputy Director, Mr. Paul Foley, Department of Occupations and Professions, 1740 Massachusetts Ave., Washington 6.

Florida: *Examination.* Miami, June 4. Sec., Mr. M. W. Emmel, Box 340, Gainesville.

Kansas: *Examination.* Kansas City, June 10-12. Sec., Dr. Leon C. Heckert, Kansas State College, Pittsburg.

Nebraska: *Examination.* Omaha, May 3-4. Sec., Mr. R. K. Kirkman, Room 1009, State Capitol Bldg., Lincoln 9.

South Dakota: *Examination and Reciprocity.* Vermillion, June 10-11. Sec., Dr. Gregg M. Evans, 310 E. 15th St., Yankton.

Washington: *Examination.* Seattle, July 13-14. Administrator, Mr. Thomas A. Carter, Department of Licenses, Capitol Bldg., Olympia.

Wisconsin: *Examination.* Milwaukee, June 4. Sec., Dr. W. H. Barber, 621 Ransom St., Ripon.

°Basic Science Certificate required.

delphia, 1894; also a dentist; specialist certified by the American Board of Internal Medicine; member of the American Clinical and Climatological Association; fellow of the American College of Physicians; in 1924 president of the New Jersey Health and Sanitary Association and the New Jersey Tuberculosis League from 1915 to 1918, and in 1955 received a citation from each; organizing president of the Essex County Tuberculosis League and a member of the Royal Institute of Public Health, London, England in 1921; captain in the medical corps of the East Orange Rifles in New Jersey during World War I and served on Emergency Medical Service of Connecticut Defense Council during World War II; at one time instructor and assistant in ophthalmology at University and Bellevue Hospital Medical College in New York City, where he was clinical assistant at New York Eye and Ear Infirmary; for many years, until his retirement, physician in charge and director of the infirmary and medical advisor in disability service and tuberculosis at the Prudential Life Insurance Company in Newark, N. J.; died Feb. 5, aged 89, of heart failure.

Culli, George Oscar, San Antonio, Texas; Barnes Medical College, St. Louis, 1908; veteran of World War I; died in the Veterans Administration Hospital Feb. 2, aged 74.

Davidson, Harold Stern Ⓜ Atlantic City, N. J.; Jefferson Medical College of Philadelphia, 1915; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; past-president of the Atlantic County Medical Society; served overseas during World War I; consultant in medicine, Atlantic City Hospital; died Feb. 18, aged 67.

Davis, Joseph Franklin, Greensboro, N. C.; Medical College of Virginia, Richmond, 1912; formerly member of the Moore County Board of Education; died in the Moses Cone Hospital Feb. 1, aged 75.

Dawson, Roger Paul Ⓜ Boston; Harvard Medical School, Boston, 1913; served on the faculty of his alma mater; selective service examiner in World War II; medical examiner for the New England Mutual Life Insurance Company until retiring; for many years associated with Massachusetts General Hospital and the Peter Bent Brigham Hospital; died in the New England Deaconess Hospital Jan. 30, aged 75.

De Young, George Marion Ⓜ Peoria, Ill.; Rush Medical College, Chicago, 1932; interned at the Illinois Central Hospital in Chicago; served a residency at the Samuel Merritt Hospital in Oakland, Calif.; veteran of World War II; at one time practiced in Georgia, Iowa, where he was a member of the school board; associated with the Peoria State Hospital; died in the Methodist Hospital Jan. 27, aged 55.

Donahey, Victor Virgil, North Hollywood, Calif.; George Washington University School of Medicine, Washington, D. C., 1936; veteran of World War II; later appointed medical director for the Atomic Energy Commission and served 18 months at Eniwetok Island in the South Pacific; died Feb. 6, aged 52.

Duncan, Cecil Earl, St. Louis; Indiana University School of Medicine, Indianapolis, 1908; died in the Veterans Administration Hospital Jan. 30, aged 72, of cerebral hemorrhage.

Emerson, Ernest Benjamin Ⓜ Rochester, N. Y.; Harvard Medical School, Boston, 1898; served as secretary of the eastern division of the American Sanatorium Association; for many years superintendent of the Rutland (Mass.) State Sanatorium; died Feb. 5, aged 86.

Epstein, Myer Ⓜ Gonzales, La.; Vanderbilt University School of Medicine, Nashville, Tenn., 1929; member of the American Academy of General Practice; coroner of Ascension Parish; died in the Baton Rouge (La.) General Hospital Feb. 3, aged 59.

Folken, Frank Garrett, Albert Lea, Minn.; University of Nebraska College of Medicine, Omaha, 1918; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology, fellow of the American College of Surgeons; veteran of World War I; on the staff of the Naeve Hospital; died Jan. 31, aged 67.

Ford, Julian C. Ⓜ Luverne, Ala.; St. Louis College of Physicians and Surgeons, 1896; died July 14, aged 85.

French, Bernard Semple Ⓜ Washington, D. C.; Johns Hopkins University School of Medicine, Baltimore, 1923; served as a member of the district commission on mental health; formerly on the faculty of Georgetown University School of Medicine; died Feb. 8, aged 72, of coronary insufficiency.

Fulton, William Everett, Akron, Ohio; Starling Medical College, Columbus, 1902; died in the Randolph Air Force Base Hospital, Texas, Feb. 4, aged 84, of pneumonia.

Gallo, Vincent Adam Ⓜ Philadelphia; Hahnemann Medical College and Hospital of Philadelphia, 1928; associated with the Philadelphia State Hospital; died Feb. 11, aged 57.

Gardner, Archibald Robert Ⓜ Lowell, Mass.; Harvard Medical School, Boston, 1902; fellow of the American College of Surgeons; associated with St. Joseph's Hospital and Lowell General Hospital; died Jan. 29, aged 79, of coronary thrombosis.

ican Otological Society and in 1949 received its Gold Medal Award of Merit; past-president of the American Academy of Ophthalmology and Otolaryngology and the Philadelphia Laryngological Society; recipient of the Newcomb Award and De Roaldes Award in 1943 and 1949, respectively; fellow of the American College of Surgeons and formerly a member of its board of governors, and the International College of Surgeons; member of the American Broncho-Esophagological Association, American Association of Immunologists, and the Association of Military Surgeons of the United States; senior consultant, American Board of Otolaryngology; served on the staffs of the Chester County Hospital in West Chester, Abington (Pa.) Memorial Hospital, Graduate Hospital of the University of Pennsylvania, Germantown Dispensary and Hospital, Presbyterian Hospital, Veterans Administration Hospital, Hospital of the University of Pennsylvania, and the Shriners' Hospital for Crippled Children; joint editor of "Ear, Nose and Throat and Their Diseases"; chief editor, *A. M. A. Archives of Otolaryngology;* died Feb. 7, aged 85.

Cobbs, Peter Price Ⓜ Los Angeles; Howard University College of Medicine, Washington, D. C., 1919; died in the Good Samaritan Hospital Feb. 1, aged 69, of injuries received in an automobile accident.

Cook, Louis E. Ⓜ Cincinnati; Medical College of Ohio, Cincinnati, 1894; a member of the Cincinnati Academy of Medicine; died in the Deaconess Hospital Feb. 4, aged 88.

Craig, Winchell McKendree Ⓜ Rochester, Minn.; born in Washington Court House, Ohio, April 27, 1892; Johns Hopkins University School of Medicine, Baltimore, 1919; interned at St. Agnes' Hospital in Baltimore; served as head of the section of neurologic surgery of the Mayo Clinic and professor of neurologic surgery in the Mayo Foundation, Graduate School, University of Minnesota; on May 27, 1957, awarded a certificate of merit by the University of Minnesota in recognition of his long service as a member of the faculty; in the same year was named director of civil defense of the city of Rochester; in June, 1959, was appointed a field representative of the Council on Medical Education and Hospitals of the American Medical Association, resigning this post in November of the same year to accept the appointment of special assistant for health and medical affairs to the Secretary of Health, Education and Welfare, United States government; past-president and secretary of the Society of Neurological Surgeons; past-president of the Harvey Cushing Society and the Association of Military Surgeons of the United States; member of the American Surgical Association, International Society of Surgery-American Branch, American Neurological Association, Western Surgical Association, Central Neuropsychiatric Association, Central Society for Clinical Research, Johns Hopkins Alumni Association, Alumni Association of the Mayo Foundation, Minnesota Surgical Society, and many others; fellow of the American College of Surgeons; in 1956 was elected president of the Mayo Foundation chapter of the Society of the Sigma Xi; served as chairman of the American Board of Neurological Surgery; member of the founders group of the American Board of Surgery; specialist certified by the American Board of Psychiatry and Neurology; veteran of World War I; in 1945 became the first physician from civilian life in the history of the U. S. Navy to reach the grade of rear admiral; having acted as organizer of the medical specialist unit of the United States Naval Reserve for many years, was called into active service in December, 1941, with the grade of commander and took his unit to the U. S. Naval Hospital, Corona, Calif., where he became chief of surgery; later transferred to the National Naval Medical Center at Bethesda, Md., where he acted as chief of surgery until October, 1945; then received his promotion to the grade of rear admiral and was transferred to the Bureau of Medicine and Surgery in Washington, D. C., as director of the graduate training program; released to civil life on Jan. 31, 1946; awarded the Legion of Merit, the Naval Reserve Medal, and the Bronze Star; served as reserve consultant to the Surgeon General of the United States Navy and as a civilian consultant to the Veterans Administration; one of the founders of the Reserve Officers of the Navy Services and served on the advisory council of that body; twice, in 1955 and 1957, was chosen by the Surgeon General of the Navy to be one of the special consultants who visited Naval medical installations in the Far East to lecture to Nava medical personnel stationed there; in November 1956, Dr. and Mrs. Craig were honored at ceremonies in Rochester conducted by neurosurgeon whom he had trained during his years of grad uate instruction in the Mayo Foundation; i March, 1957, was invited to deliver the Georg M. Kober Memorial Lecture at Georgetown Un versity, Washington, D. C.; a member of th board of trustees of the Ohio Wesleyan Unive sity, Delaware, Ohio, which awarded him th honorary degree of doctor of science in 1937; member of the editorial staff of *The Journal* *Neurosurgery* and of the special advisory boa to *Postgraduate Medicine;* in 1956 completed a published a volume on the genealogy of the Cra family in America; died in St. Mary's Hospit Feb. 12, aged 67, of a brain tumor.

Crankshaw, Charles William, Hartford, Conn.; bo in Conshohocken, Pa., Sept. 14, 1870; Universi of Pennsylvania Department of Medicine, Phi

School of Medicine; veteran of World Wars I and II; associated with Kentucky Baptist Hospital, Norton Memorial Infirmary, and St. Joseph Infirmary; died Feb. 5, aged 65.

Jones, Evan L. Ⓜ Philipsburg, Pa.; Baltimore Medical College, 1898; for many years school physician; member of the staff of the Philipsburg State Hospital; died in the Hollidaysburg (Pa.) State Hospital Feb. 1, aged 90.

Kahn, Ernest Arthur, Deerfield, Ill.; University of Illinois College of Medicine, Chicago, 1937; member of the American Society of Anesthesiologists and the American Academy of General Practice; died Jan. 21, aged 50.

Kunz, Harold George Ⓜ Montclair, N. J.; Jefferson Medical College of Philadelphia, 1937; interned at the Mountainside Hospital; veteran of World War II; fellow of the American College of Surgeons; senior attending surgeon at Crippled Children's Hospital in Newark; served on the staffs of the Mountainside, St. Vincent's, and Community hospitals; died in the Harkness Pavilion of the Columbia–Presbyterian Medical Center in New York City Feb. 5, aged 48.

Laird, Leslie Allen Ⓜ Richmond, Ind.; Indiana University School of Medicine, Indianapolis, 1931; served as county coroner; a staff member of Richmond State Hospital; died Jan. 30, aged 65.

Lasday, Louis Ⓜ Pittsburgh; University of Pittsburgh School of Medicine, 1911; veteran of World War I; served many years as a physician for the city board of education; died in the Montefiore Hospital Feb. 1, aged 66, of congestive heart failure.

Latcher, Marshall, Oneonta, N. Y.; Albany (N. Y.) Medical College, 1897; associated with the Aurelia Osborn Fox Memorial Hospital, where he died Jan. 13, aged 90, of arteriosclerotic heart disease.

Lawton, Richard John Ⓜ Terryville, Conn.; Maryland Medical College, Baltimore, 1908; specialist certified by the American Board of Dermatology; member of the American Academy of Dermatology and Syphilology; served overseas during World War I; associated with St. Mary's Hospital in Waterbury, Waterbury (Conn.) Hospital, Charlotte Hungerford Hospital in Torrington, and the Bristol (Conn.) Hospital, where he died Feb. 5, aged 76.

Lockwood, William Edison, Slater, Mo.; National University of Arts and Sciences Medical Department, St. Louis, 1917; veteran of World War I; died in the John Fitzgibbon Memorial Hospital, Marshall, Jan. 31, aged 68.

Long, Henry, Sheffield, Ala.; Meharry Medical College, Nashville, Tenn., 1920; died in the Colbert County Hospital Jan. 27, aged 65.

MacFadyen, Paul Rutherford, Concord, N. C.; University of Virginia School of Medicine, Charlottesville, 1929; died Feb. 3, aged 56, of third degree burns.

Mansell, Chris C. Ⓜ Lubbock, Texas; University of Tennessee College of Medicine, Memphis, 1928; veteran of World War II; associated with the West Texas Hospital; died Jan. 30, aged 56.

Marsteller, Emlyn H., Ⓜ Manassas, Va.; Medical College of Virginia, Richmond, 1902; for many years county coroner; a two-term member of the Prince William County school board; died in the Doctors Hospital, Washington, D. C., Feb. 13, aged 82.

McFadden, Patrick John Ⓜ Erie, Pa.; Jefferson Medical College of Philadelphia, 1925; veteran of World War II; member of the staff of the Veterans Administration Hospital; died in January, aged 58.

McQuilkin, George A. Ⓜ Varysburg, N. Y.; Northwestern University Medical School, Chicago, 1905; past-president of the Wyoming County Medical Society; served as health officer and school physician; member of the staff of the Wyoming County Community Hospital, Warsaw, where he died Jan. 30, aged 79.

Mesirow, Maurice Elias Ⓜ San Francisco; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1907; specialist certified by the American Board of Ophthalmology; member of the American Academy of Ophthalmology and Otolaryngology and the Association for Research in Ophthalmology; served on the staff of Our Lady of Perpetual Help Hospital in Santa Maria; died in Franklin Hospital Jan. 29, aged 73.

Moles, Joseph Ⓜ Oak Forest, Ill.; Chicago College of Medicine and Surgery, 1917; died Jan. 28, aged 68.

Moran, Vincent Domeet Ⓜ Buffalo; University of Buffalo School of Medicine, 1930; specialist certified by the American Board of Orthopaedic Surgery; member of the American Academy of Orthopaedic Surgeons; fellow of the American College of Surgeons; associated with the Emergency Hospital, Edward J. Meyer Hospital, Sisters of Charity Hospital, Millard Fillmore Hospital, and St. Francis Hospital; died in the Edward J. Meyer Hospital Jan. 27, aged 52.

Morgan, Perry L. Ⓜ North Ridgeville, Ohio; Cleveland Homeopathic Medical College, 1900; veteran of the Spanish–American War; associated with the Elyria (Ohio) Memorial Hospital; died Jan. 19, aged 81, of coronary occlusion and diabetes mellitus.

Gavaris, George Procopios Ⓜ Chicago; National University of Athens School of Medicine, Greece, 1907; died Feb. 9, aged 73, of acute coronary occlusion.

Gingles, Hunter Watkins Ⓜ Bowling Green, Ky.; University of Louisville (Ky.) School of Medicine, 1915; died in the Bowling Green–Warren County Hospital Feb. 5, aged 70, of coronary thrombosis.

Goff, Gomer Flow Ⓜ Dallas, Texas; Johns Hopkins University School of Medicine, Baltimore, 1921; member of the Central Association of Obstetricians and Gynecologists; fellow of the American College of Surgeons; clinical associate professor of obstetrics and gynecology, University of Texas Southwestern Medical School; consultant, Baylor University Hospital; died Feb. 3, aged 65.

Gramlich, Henry Frank Ⓜ Long Beach, Calif.; University of Buffalo School of Medicine, 1920; veteran of World War I; died Feb. 4, aged 62.

Greenbaum, Roy, St. Louis; Washington University School of Medicine, St. Louis, 1934; served an internship and residency at St. Louis City Hospital; veteran of World War II; died Feb. 8, aged 50.

Greene, Henry Lewis Ⓜ Madison, Wis.; University of Oregon Medical School, Portland, 1928; specialist certified by the American Board of Orthopaedic Surgery; member of the Clinical Orthopaedic Society and the American Academy of Orthopaedic Surgeons; fellow of the International College of Surgeons and the American College of Surgeons; past-president of the Wisconsin Orthopedic Society; associated with Madison General and St. Mary's hospitals; died in Tucson, Ariz., Feb. 3, aged 59.

Greene, Marvin Louis Ⓜ Monticello, Ga.; University of Georgia Medical Department, Augusta, 1949; interned and served a residency at the Charity Hospital of Louisiana in New Orleans; served as president of the Jasper County Medical Society; a director of the Monticello–Jasper County Junior Chamber of Commerce; member of the Monticello Chamber of Commerce; died in the Jasper Memorial Hospital Feb. 4, aged 35.

Hampton, William Milford, Greensboro, N. C.; Meharry Medical College, Nashville, Tenn., 1938; interned at the City Hospital in Winston–Salem; served a residency at the L. Richardson Memorial Hospital; for many years a member of the city council and school board; died Feb. 9, aged 47.

Harriman, Frank Edwin, Worcester, Mass.; Tufts College Medical School, Boston, 1916; fellow of the American College of Surgeons; veteran of World War I; associated with the Worcester City Hospital; died Feb. 5, aged 66.

Harris, Lyndon Denny Ⓜ Chicago; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1912; served on the faculty of his alma mater; member of the American Academy of General Practice; died in the Garfield Park Community Hospital Feb. 15, aged 71.

Harrison, Bruce Ashton Ⓜ Colchester, Ill.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1909; veteran of World War I; died in Macomb Feb. 3, aged 73.

Haubrich, Bernard Page Ⓜ Claremont, N. H.; Boston University School of Medicine, 1927; veteran of World Wars I and II; past-president of the Sullivan County Medical Society; served as school physician; on the staff of the Claremont General Hospital, where he died Jan. 29, aged 60.

Hickerson, John C. Ⓜ Independence, Mo.; Beaumont Hospital Medical College, St. Louis, 1899; for many years associated with the Independence Sanitarium and Hospital, where he died Feb. 4, aged 85.

Hill, Frank Russell Ⓜ Cleveland; University and Bellevue Hospital Medical College, New York City, 1931; served an internship and residency at St. Luke's Hospital, where he was on the staff; veteran of World War II and won a Bronze Star medal for meritorious service; died Feb. 2, aged 54.

Hyatt, Anderson Lawrence, Kinston, N. C.; University of Maryland School of Medicine, Baltimore, 1910; veteran of World War I; formerly member of the county board of health; died Feb. 3, aged 75.

Johnson, Arthur Charles Ⓜ Omaha; University of Minnesota Medical School, Minneapolis, 1921; fellow of the American College of Surgeons; clinical professor of surgery at Creighton University School of Medicine; formerly a fellow in surgery at the Mayo Foundation in Rochester, Minn.; on the staffs of St. Catherine's, St. Joseph's, Clarkson, Immanuel, Children's, and Doctors hospitals; died Feb. 3, aged 65.

Johnson, William Oscar Ⓜ Louisville, Ky.; born in 1894; Johns Hopkins University School of Medicine, Baltimore, 1920; specialist certified by the American Board of Obstetrics and Gynecology; member and past-president of the American Association of Obstetricians and Gynecologists, Central Association of Obstetricians and Gynecologists, and the Southern Gynecological and Obstetrical Society; past-president of the Louisville Obstetrical and Gynecological Society and the Kentucky Obstetrical and Gynecological Society; past-vice-president of the Kentucky State Medical Association; past-president of the Kentucky Wesleyan Alumni Association; fellow of the American College of Surgeons; served on the faculty of the University of Louisville

Rosenwald, Gertrude, Park Ridge, Ill.; Universität Bern Medizinische Fakultät, Switzerland, 1937; died Feb. 13, aged 49.

Rossi, Frank John, Utica, N. Y.; Universita di Napoli Facolta di Medicina e Chirurgia, Italy, 1910; fellow of the American College of Surgeons; associated with St. Luke's–Memorial Hospital Center and St. Elizabeth Hospital; past-president of the Oneida County Medical Society; died Jan. 20, aged 85.

Rothman, Joseph, Lake Placid, Fla.; St. Louis University School of Medicine, 1915; veteran of World Wars I and II; served on the staffs of various Veteran Administration hospitals; died in the Walter Reed Army Hospital, Washington, D. C., Jan. 22, aged 66.

Ruggieri, Rosario C., Eastville, Va.; Universita di Napoli Facolta di Medicina e Chirurgia, Italy, 1899; served as Italian consul at Norfolk, where he practiced for many years; died Jan. 29, aged 85.

Runkle, Stuart Calvin Jr., Waupun, Wis.; Jefferson Medical College of Philadelphia, 1932; interned at Methodist Episcopal Hospital in Philadelphia; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychiatric Association; veteran of World War II; later served in the regular U. S. Navy; associated with the Wisconsin State Prison Hospital; died in St. Agnes Hospital, Fond du Lac, Oct. 10, aged 56, of acute myocardial infarction.

Schuyler, Dora Rochelle, St. Louis; Barnes Medical College, St. Louis, 1910; died in Berkeley, Mo., Jan. 20, aged 74.

Sease, John Claude Ⓐ Newberry, S. C.; Medical College of South Carolina, Charleston, 1917; past-vice-president of the South Carolina Medical Association; past-president of the South Carolina Public Health Association; secretary-treasurer of the Newberry County Medical Society, of which he was past-president; veteran of World War I; health officer of Newberry, Laurens, and Union counties; died Jan. 31, aged 67.

Selleck, Ernest Edward, East Orange, N. J.; Columbia University College of Physicians and Surgeons, New York City, 1902; died Jan. 25, aged 83.

Siler, Joseph Franklin Ⓐ Colonel, U. S. Army, retired, Washington, D. C.; born in Orion, Ala., June 8, 1875; University of Virginia School of Medicine, Charlottesville, 1898; following an internship at the New York Post-Graduate Hospital in New York City, entered the Army Medical Service during the Philippine Insurrection in 1900 as a contract surgeon; commissioned a first lieutenant in the regular Army in 1903; in 1905 returned to the Philippines, serving there until 1907; in 1908 assigned to Fort Slocum, New York City; in 1912 appointed chairman of a pellagra commission organized by the New York Post-Graduate Hospital, and travelled throughout the Southern United States and the Caribbean in connection with this study; during World War I, after going to France as commanding officer of Base Hospital number 8, was reassigned to organize the division of laboratories and infectious diseases for the American Expeditionary Forces; returned to Washington, D. C., as chief of the preventive medicine division and laboratories in the Army Surgeon General's Office; during 1923-1925 returned for the third time to the Philippines as chief of the medical department research board to study the transmission of dengue fever; director of preventive medicine to the Surgeon General's Office from 1925 to 1929, at which time he went to the Panama Canal Zone as chief health officer; before retiring from the Army Medical Service on June 30, 1939, served five years as commandant of the Army Medical School (now the Walter Reed Army Institute of Research); it was during this period that he made his investigations of immunization to typhoid fever; in 1941 recalled to active duty for two years as a member of a retiring board at Walter Reed Army Medical Center; among his many honors were the Distinguished Service Medal, and the Kober Award, granted by Georgetown University for distinguished service in preventive medicine in 1939; named Comendador in the Order of Vasco Nunez de Balboa by the Republic of Panama; member of the House of Delegates of the American Medical Association in 1921, 1927, 1936, 1937, and 1938; specialist certified by the American Board of Preventive Medicine; member of the National Board of Medical Examiners from 1934 to 1947; a member and past-president of the American Society of Tropical Medicine; member of the American Association for the Advancement of Science, Washington Academy of Medicine, American Public Health Association, and the Association of Military Surgeons; fellow of the American College of Surgeons and the American College of Physicians; founder, member, and served as president of the Gorgas Memorial Institute of Tropical and Preventive Medicine, and was secretary and later president of the Walter Reed Memorial Association; a major contributor in developing a simpler and more effective typhoid vaccine; died Feb. 7, aged 84.

Small, Vincent M. Ⓐ Gallatin, Tenn.; University of Tennessee College of Medicine, Memphis, 1950; interned at Methodist Hospital in Indianapolis; district health officer of Macon–Robertson–Sumner–Trousdale counties; veteran of World War II; died in the Vanderbilt University Hospital, Nashville, Jan. 26, aged 44.

Muir, Ian Wildridge, Big Spring, Texas; Medical College of Alabama, Birmingham, 1951; interned at the Carraway Methodist Hospital in Birmingham, Ala.; veteran of World War II; served as a member of the staffs of the Big Spring State Hospital and the Veterans Administration Hospital; formerly associated with the San Antonio (Texas) Tuberculosis Hospital; died Feb. 4, aged 39.

Murray, Leo Charles Ⓜ Los Angeles; Washington University School of Medicine, St. Louis, 1924; died Jan. 29, aged 60.

Naeckel, Harold William Ⓜ Riverside, Calif.; Indiana University School of Medicine, Indianapolis, 1925; associated with the Riverside Community Hospital; died in the University of California Health Center in Los Angeles Jan. 29, aged 62.

Neiswander, Leo Clair, Ada, Ohio; Ohio State University College of Homeopathic Medicine, Columbus, 1915; veteran of World War I; died Jan. 28, aged 71, of amyotrophic lateral sclerosis.

Nye, George Earl Ⓜ Scottsboro, Ala.; Chattanooga (Tenn.) Medical College, 1906; veteran of the Spanish-American War and World War I; served as surgeon for the Southern Railway; died Jan. 31, aged 84.

Odom, John Darby Ⓜ Dothan, Ala.; Emory University School of Medicine, Atlanta, Ga., 1916; for many years associated with the Immigration Department of the Panama Canal Zone; veteran of World War I; died Jan. 9, aged 69.

O'Kelley, Henry Thomas, Portageville, Mo.; Barnes Medical College, St. Louis, 1910; veteran of World War I; died in the Veterans Administration Hospital in Poplar Bluff Jan. 8, aged 74.

O'Neill, Francis William Ⓜ Spokane, Wash.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1905; past-president of the Spokane County Medical Society; once served as president of the medical staff of Sacred Heart Hospital, where he died Jan. 21, aged 79.

Owen, William Roy Ⓜ Osage, Iowa; State University of Iowa College of Homeopathic Medicine, Iowa City, 1903; died Jan. 18, aged 82.

Pender, George Edward Ⓜ Portsmouth, N. H.; New York University Medical College, New York City, 1897; served as health officer and as chairman of the health board; died Jan. 25, aged 87.

Phillips, Robert Alan Ⓜ Pasadena, Calif.; University of Nebraska College of Medicine, Omaha, 1925; died Feb. 6, aged 59.

Poorman, Bertram Allen Ⓜ Kansas City, Mo.; University Medical College of Kansas City, Mo., 1903; fellow of the American College of Surgeons; associated with the Kansas City General Hospital; on the staffs of the St. Joseph Hospital and Queen of the World Hospital; died in the Neurological Hospital Jan. 20, aged 81.

Porter, John E., Stevensville, Mont.; Rush Medical College, Chicago, 1895; died Jan. 21, aged 92.

Quattlebaum, Leon, Harbor City, Calif.; University of Arkansas School of Medicine, Little Rock, 1946; interned at the Medical and Surgical Memorial Hospital in San Antonio, Texas; served a residency at the Baptist Memorial Hospital in San Antonio, Texas, and the University Hospital in Little Rock, Ark.; an officer in the medical corps, Army of the United States, from August, 1947, to July, 1949; associated with the Kaiser Hospital; died Jan. 25, aged 36.

Ragins, Alex Benjamin Ⓜ Chicago; born in Kiev, Russia, Feb. 6, 1907; University of Illinois College of Medicine, Chicago, 1932; interned at the Kankakee State Hospital in Kankakee, Ill., and the Cook County Hospital in Chicago, where he served a residency; specialist certified by the American Board of Pathology; member of the American Association of Pathologists and Bacteriologists, College of American Pathologists, and the American Society of Clinical Pathologists; veteran of World War II; on the faculty of his alma mater; associated with the Cook County Hospital; died in the Oak Forest (Ill.) Hospital Feb. 14, aged 52.

Ramsaur, Charles Stewart, Dallas, Texas; Baylor University College of Medicine, Dallas, 1927; veteran of World War I; died Jan. 27, aged 65.

Red, William Stuart Jr., Houston, Texas; University of Texas School of Medicine, Galveston, 1925; died in St. Joseph's Hospital Jan. 17, aged 61.

Reynolds, John, Muskogee, Okla.; Louisville (Ky.) Medical College, 1903; died Dec. 26, aged 85, of carcinoma of the liver.

Roelkey, Francis Daniel, Uniontown, Pa.; Maryland Medical College, Baltimore, 1905; died Jan. 16, aged 81, of congestive heart disease.

Rogers, John C. Ⓜ Henderson, Ky.; Rush Medical College, Chicago, 1931; veteran of World War I; health officer for Henderson, Union, and Webster counties; chairman of the Henderson County Board of Health; associated with Methodist Hospital; died Jan. 31, aged 64.

Rogers, Thomas Edward Ⓜ Macon, Ga.; Atlanta College of Physicians and Surgeons, 1910; fellow of the American College of Physicians; past-president of the Bibb County Medical Society; an honorary member of the Macon Hospital staff; died Jan. 19, aged 73.

BRAZIL

Hofstaetter's Syndrome.—Drs. Mirra and Acquesta (*Rev. paulista med.* 55:355, 1959) reported a series of 44 patients with Hofstaetter's syndrome, or premenarchal mammary asymmetry. Knowledge of this relatively rare condition should help to prevent an erroneous diagnosis of tumor of the breast. Most observers believe that the difference in development of the two breasts is the result of an excessive response of the larger to stimulation from the estrogenic hormone and not of inadequate or insufficient response of the other gland. The age of the patients varied between 5 and 12 years (average 8.9 years). In 40 patients the presence of the enlargement was the reason for seeking medical advice, and in 4 the reason was pain. The fear of a malignancy was the most important reason for 34 of the families to bring their child to the clinic. Pain was present in 30 patients and pruritus in 1. As a rule the enlarged breast had a discoid form with definite outlines, smooth surface, firm or hard consistency, and perfect mobility. Palpable lymph nodes were present in 12 but were not considered significant. The symptoms disappeared within one or two years. The presence of the syndrome did not influence the onset of the menarche, which began normally.

ECUADOR

Prefrontal Leukotomy.—At the meeting of the Academia Ecuatoriana de Medicina in July Dr. Gustavo Endara presented a report on a series of 25 psychiatric patients on whom prefrontal leukotomy was performed. Preoperative care, especially the control of temperature, pulse, respirations, and blood pressure, was necessary in these patients in order to evaluate the patient's condition in the immediate postoperative period. Local anesthesia was used for all patients. Postoperative confusion and lethargy replaced anxiety, tension, depression, melancholy, and agitation for the first few days, but memory and attention gradually improved, and a feeling of well-being and even euphoria was established. The results were satisfactory, especially in patients with agitation and anxiety. The main postoperative side-effects were somnolence, in 21, and urinary incontinence, in 6. These side-effects disappeared within a few days. One patient developed a cerebral abscess and died. Prefrontal leukotomy was thus found to be a good therapeutic procedure when all other nonsurgical measures proved unsuccessful.

FRANCE

Thiomucase: a New Spreading Factor.—A. Castaigne (*Anesth. Analg. Réanimation,* no. 3, 1959) found that different hyaluronidase preparations which had the same titer in turbidimetric units did not have the same effect on experimental animals and human beings. He therefore isolated a fraction that had an in vivo spreading action but none of the hyaluronidase effects in vitro. He investigated the substances on which these fractions had an effect and found that the spreading action was caused by the depolymerization of chondroitinsulfuric acid. The new principle was called thiomucase. Hyaluronidase and thiomucase are different enzymes.

The author studied the spreading action of thiomucase and of hyaluronidase on the skin of rats and showed that the thiomucase effect was twice as great as that of hyaluronidase. Thiomucase has also a more powerful effect than hyaluronidase. Thiomucase has also a more powerful effect than hyaluronidase on the subcutaneous tissular pressure, and it promotes a more definite acceleration of subcutaneous reabsorption. When injected around the articulation, thiomucase shows a marked penetrating effect which does not exist in hyaluronidase. The same difference was found in intra-articular diffusion. On the other hand, heparin completely inhibits the hyaluronidase spreading action but does not affect the thiomucase action.

The Virus of the Cytomegalic Inclusion Disease.—At a meeting of the Académie Nationale de Médecine, M. Lelong and co-workers reported that they had isolated, cultivated, and photographed the virus responsible for cytomegalic inclusion disease in two newborn infants. This study confirmed the studies of Smith, Rowe, and Weller. The neonatal disease was characterized by hepatosplenomegaly, deep icterus, hemorrhage, and platelet deficiency and resembled hemolytic disease of the newborn infant. The virus was isolated from saliva, tears, and urine. The isolation and maintenance of this virus was possible only on fibroblasts of human origin. One of the infants observed recovered without any sequels. In an apparently healthy woman whose newborn infant died shortly after birth, the authors could detect typical inclusion cells in the placental villi, thus demonstrating the necessity of an early detection of a disease which may be transmitted through the placenta and cause a fatal infection in the fetus or in the newborn infant.

Psilocybin.—J. Delay and co-workers (*Presse méd.,* Oct. 24, 1959) gave psilocybin to 20 normal volunteers. The first reaction was headache with asthenia, and then a feeling of euphoria, dreamlike disorders of the consciousness, and delirium occurred. The subjects discovered a magic universe which seemed to be the realm of fundamental truth and pure beauty. This state lasted three to six hours. On the other hand, there were a diffuse sensation of malaise and emotional abreactions. Sometimes there were dissociations of consciousness which favored

FOREIGN LETTERS

AUSTRIA

Austrian Physicians Protest.—On Feb. 23, the representatives of the Chamber of the Austrian Physicians, under the leadership of their president, Dr. Eberle, called on the Federal Chancellor to protest the unsatisfactory course of the negotiations between the Chambers of the Physicians and the Sick Insurance Funds. These concerned demands of the physicians, formulated in 1957, which have not yet been fulfilled. The representative stated that if by March 31 no satisfactory agreement is achieved, no contract concerning fees for District, Agricultural, and Trade Sick Insurance Funds will remain in force. The Sick Insurance Funds have refused to fulfill the demands of the physicians so far because of their financial difficulties, although they have repeatedly admitted that the demands are justified. The Federal Chancellor pointed out that the problems of the Sick Insurance Funds come within the jurisdiction of the Federal Minister for Social Administration and that the Minister should make suggestions for clearing up the situation. The Chancellor, however, stated that he would be ready to take up negotiations concerning these problems. He acknowledged the justice of the desire of the doctors for adequate fees for the services given to the Sick Insurance Funds and promised to have the problem discussed at the next session of the Council of Ministers.

Cranial Trauma.—At the meeting of the Society of Physicians in Vienna on Dec. 11, F. Gerstenbrand emphasized that the treatment of traumatic lesions of the brain requires close cooperation between surgeon, anesthetist, and neurologist. E. Amann and G. Salem stated that emergency measures include tracheotomy, treatment of threatened circulatory failure, protection against cerebral edema, removal of motor unrest (particularly of tetanic spasms with the lytic cocktail), and administration of thiopental. If unconsciousness is prolonged, control of water and electrolyte metabolism is important. If there is increase in temperature, the temperature should be restored to normal as rapidly as possible. In the last two years the speakers were successful in keeping alive 45 of 83 persons with severe cranial trauma by means of these measures.

K. Holub pointed out that, in the presence of a so-called cellular hyperhydration, administration of ACTH and cortisone may exert a favorable effect. In the presence of cellular dehydration the administration of posterior pituitary preparations is indicated. O. Mayrhofer pointed out the significance of tracheotomy with respect to reducing the risk of cerebral edema.

New Therapeutic Possibilities in Rhinology.—At the same meeting K. Burian reported on a series of animal experiments concerning the effect of stress on the behavior of the nasal mucosa and various local injuries of the mucosa. On the basis of examination of acute and chronic lesions it was proved that the mucosa adapts to slowly increasing concentrations of an injurious agent and simultaneously develops increasing resistance to this agent and also to other damage. One has, therefore, to deal with a nonspecific process. This phenomenon of increased resistance through adaptation to an injurious agent was confirmed also by industrial-hygienic studies carried out in industrial plants working with gaseous formaldehyde and ammonia. On the basis of these observations, made in the course of animal experiments, a new therapeutic method was proposed which consists of local adaptation therapy with slowly increased concentrations of a mildly injurious agent. In the clinic this therapy is applied at present for three purposes, namely, to influence the mode of reaction of the nasal mucosa in patients with vasomotor diseases; to influence local allergic reactions of the nasal mucosa; and to treat acute coryza. L. Hoffmann confirmed from the clinical point of view the effectiveness of acid vapors on coryza. Particularly effective is formic acid, but so also is fresh onion vapor.

O. Kraupp stated that the degree and the type of the local effect of formaldehyde depends essentially on the concentration of the substance in the inspired air: the changes of the surfaces of the mucosa can comprise all degrees of protein denaturation, from the precipitation which is localized at the marginal plane (astriction) to the erosion of deep layers. One could consider that pretreatment with slowly increasing concentrations of formaldehyde vapor might effect a systematic tanning of the respiratory mucosa which then would provide a certain protection against the necrotizing and locally stimulating effect of higher concentrations of formaldehyde. The protective effect of pretreatment with formaldehyde for the local erosive effect of ammonia vapors could be similarly interpreted. Furthermore such substances as formic acid and zinc sulfate, the anti-inflammatory effects of which were observed by the speaker, possess a strong astringent action.

The items in these letters are contributed by regular correspondents in the various foreign countries.

The number of attacks was found to be unaffected by the various treatments. The measure of effectiveness finally chosen was the total number of days off work due to attacks conforming to the definition of bronchitis during the trial. Both antibiotics cut the time off work in half but did not differ significantly from each other. The average monetary losses per patient in the three groups through time off work were: penicillin group, $42; tetracycline group, $54; and control group $120. The cost of treatment for four months was $96 for patients in the tetracycline group and $48 for patients in the penicillin group. Thus the net cost of illness in the three groups was $90 in the penicillin group, $150 in the tetracycline group, and $120 in the control group that received no medication. There was thus a net gain of $30 per patient in the penicillin group and a net loss of $30 in the tetracycline group. It was concluded from the trial that penicillin and tetracycline are equally efficacious in reducing the duration but not the number of attacks of bronchitis.

Cold Injury in Newborn Infants.—Due to general absence of central heating in Britain and the low temperatures at night in bedrooms, many babies are admitted to hospitals suffering from cold injury. This can be fatal, particularly in those with congenital heart disease. Bower and co-workers (*Brit. M. J.* 1:303, 1960) stated that of 183 hypothermic babies admitted to a Birmingham Hospital, 70 were suffering from primary cold injury and not from disease. Special low-reading thermometers were used, as some of the babies, when admitted, had temperatures as low as 80 F (26.7 C). A typical history was that the baby was kept in a room with a coal fire, which was allowed to die out at night, or with an electric space heater which was switched off when the family went to bed. Sometimes the baby's cot was next to a drafty window. A few of the cases occurred when the baby was born into cold surroundings before the arrival of the doctor or midwife. Tight blankets restricting movement were also a factor.

The commonest manifestation was edema, noted in 89% and present on the cheeks, buttocks, and limbs. Facial erythema occurred in 44% and cyanosis in 16%. Unfortunately the former conveyed an impression of health to the unwary observer. The situation was analogous to that in pink disease, where the cold extremities were often pink rather than cyanotic. Sclerema, which is induration and rigidity of the skin, with loss of softness and pitting on pressure, occurred in 27%; 59% of the babies were immobile. The rectal temperatures of the babies ranged from 80 to 94 F (26.7 to 34.4 C). Most were between 84 and 92 F (28.9 and 33.3 C). There was a striking preponderance of male babies. The only abnormal laboratory findings were a raised blood urea level and oliguria.

It was found that rapid warming of the babies led to hyperthermia and convulsions. Therefore the body temperature was raised gradually over a period of several days. In some cases this took over a week. The babies, fully clothed, were put into a cot in a cubicle maintained within the temperature range of 65 to 70 F (18.1 to 21.1 C). They were slowly warmed, as it was considered undesirable that peripheral metabolism should be increased before that of the brain and thoracic organs. Prophylactic antibiotics and additional glucose in gastric feedings were given, although it was not known whether or not these were necessary. Eighteen babies died, a mortality of 26%. At autopsy the commonest finding was massive pulmonary hemorrhage. Follow-up studies were made of 36 babies, and only 3 had disabilities which might possibly have been due to chilling (cerebral palsy, mild mental retardation, and epilepsy) although these may have been coincidental.

Byssinosis and Histamine.—Byssinosis is a condition common in cotton mill workers, with dyspnea and a feeling of tightness in the chest as its main symptoms. These are most prominent when the workers return to the mills after a few days' absence. The respiratory symptoms are generally ascribed to the inhalation of the dust produced in the cardrooms of the mills. Bouhuys and co-workers (*Brit. M. J.* 1:324, 1960) studied the effect of cotton dust on the pulmonary ventilation of men not previously exposed to cotton mill dust. Extracts of the dust were inhaled in the form of an aerosol, and the changes produced in lung ventilation were studied by examination of nitrogen clearance. This involves the continuous recording of the nitrogen concentration in expired gas during oxygen breathing. The lung clearance index is the amount of ventilation required to wash out the nitrogen from one liter of the lung volume down to 2% nitrogen in the end-tidal gas. The index is increased in asthmatic and in normal subjects after the inhalation of histamine.

It was found that inhalation of cotton dust extract increased the lung clearance index although house dust extract did not. The effect of the cotton dust extract on the index did not occur after repeated inhalation, but after a rest period of several days the effects were again reproducible. This was analogous to what happened to the workers *in the cotton mills. Animal experiments suggested* that this effect was not due to the liberation of histamine, as had been suggested, but to the formation of a histamine liberator which was detected in the cotton duct extract. It was believed that the symptoms of byssinosis were due to the histamine liberator in cotton dust and not to the direct antigen-antibody reaction in the lungs leading to the formation of histamine.

the revival of traumatic memories from childhood. The most dramatic phenomena were of a psychosensory type in the visual field, such as the perception of colors with alterations of light and contrast, followed by a state of esthetic enjoyment. Some of these disorders developed into hallucinations.

The authors tried psilocybin as a therapeutic agent and obtained some neurovegetative modifications in paranoid patients. In hebephrenic patients an atypical agitation was observed. In paranoic patients who had had recent onset violent reactions occurred with confused states that constituted a real psychodrama. According to the authors the psilocybin test is valuable in patients with neuroses and emotional imbalance. In hysteriacs the amnesia sometimes disappeared as a result of taking psilocybin, and the patients were able to recall events of their childhood. In patients with obsessions the reaction was intense and rapid. They first felt anxiety and then guilt feelings and aggression. In psychopaths the behavior changed rapidly and continuously, passing from a theatrical attitude to passive resistance and hostility. Sometimes the lifting of inhibitions gave the physician valuable information. Often the patients themselves recognized the value of the psilocybin test.

INDIA

Urinary Calculi.—P. Das studied a series of 82 patients with urinary calculi (*J. Indian M. A.*, vol. 34, Jan. 16, 1960). Congenital anomalies were present in 9 of the 27 patients operated on, and in 7 of these they could have contributed to the formation of calculi. These abnormalities included bifid pelvis, narrowing of the pelviureteral junction, horseshoe kidney, aberrant renal artery, ectopia vesicae, congenital vesicovaginal fistula, and intrarenal pelvis. To determine the incidence of infection which could contribute towards calculus formation, urine was examined for pus cells in all patients and cultured in some. A single routine examination of urine showed pus cells in all but two. Urine culture was done in eight and showed positive results in five. The cultures showed Escherichia coli in three, Pseudomonas in one, and Streptococcus faecalis in one.

Reappearance of calculi after removal occurred in three patients. All had narrowing of the pelviureteral junction, one had in addition an aberrant renal artery, and another had a completely intrarenal pelvis. In the two patients with urethral calculi, the stones became impacted while being voided in the urinary stream. Thus the study showed that narrowing of the pelviureteral junction played an important part in the formation and recurrence of calculi. Narrowing leads not only to stasis but also prevents passage of small concretions which would otherwise have passed out. Seven of the 27 patients with renal calculi who were operated on showed such stenosis to a marked extent, and one had an epidermoid carcinoma blocking the pelvic outlet. Two patients had moderate narrowing, two had well-formed aberrant renal artery, and in one the bridge of the horseshoe kidney prevented free flow of urine. As regards the mechanism of formation of these stones, one patient showed definite evidence of formation of stones by coalescence of crystals. Another had a stone attached to a renal papilla. This stone also showed ossification. There was no evidence of stone formation from microliths in the series. Nine of the 30 patients with vesical calculi had chronic urethral obstruction, 2 were malnourished, and 1 had an associated cystitis cystica.

After-Care Colony for Tuberculous Patients.—The first organized after-care colony and rehabilitation center for tuberculous patients in India was opened in West Bengal in December, 1959, about 100 miles from Calcutta. It occupies an area of 222 acres near the government tuberculosis sanatorium and is connected with the nearest towns by railroads. Arrangements are made to accommodate 50 families in 25 blocks, each with two cottages. The planners envisage setting up cottages and workshops where former tuberculous patients can improve their health and also earn a living.

UNITED KINGDOM

Cost of Treating Chronic Bronchitis.—Chronic bronchitis is annually responsible for the loss of 22 million working days among men in England and Wales, representing 25% of all male sickness incapacity. Its economic treatment, therefore, is a matter of importance to employers and to the Ministry of Health, which pays for most of the drugs used. A trial, sponsored by the Medical Research Council, was organized by Francis and Spicer (*Brit. M. J.* 1:297, 1960) to compare the effectiveness and comparative costs of tetracycline and penicillin as long-term prophylactics in chronic bronchitis. A series of 252 men with the condition were randomly allocated to three matched groups. Each patient in group 1 was given 250 mg. of tetracycline twice daily; in group 2 each was given 312 mg. of potassium penicillin V twice daily; and in group 3 an inert capsule was given twice daily. All were identical in appearance and were given prophylactically for four months during the winter. The effectiveness of treatment was judged by comparing the number of attacks of bronchitis during the period of treatment, the duration of the attacks, the number of days off work, and the money lost while away from work.

tion of these patients respond by complete remissions either to no therapy at all or to conventional doses of the corticosteroids. Some of our patients who did not respond to conventional doses have had complete remissions after being given steroid therapy in large or massive doses of 50 to 150 mg. of prednisone daily (Dameshek and others, *J. A. M. A.* 166:1805 [April 12] 1958). As for splenectomy, it is also clear that some patients show only a minor response to this operation, relapsing either shortly thereafter or after several months or even years. The relapse rate in our series was more than 50% (Stefanini and Dameshek: Hemorrhage Disorders: Clinical and Therapeutic Approach, New York, Grune & Stratton, 1955).

Thus it behooves the practicing physician to observe the patient with ITP over a fairly lengthy period, perhaps up to a year, as the data of Carpenter and his associates imply. During this waiting period such medical treatment as fresh blood transfusions and administration of platelet rich plasma and of adequate doses of the corticosteroids may be given. (What constitutes an adequate dose varies with the patient; it may be 40 mg. of prednisone, the maximum dose in Carpenter's series, or it may be 140 mg.) These are almost always successful in coping with the bleeding problem, and one is often rewarded by a return of the platelet count to the normal level, even in patients over 30 years of age. Splenectomy may have to be performed, but this major operation is by no means to be entered into lightly or with haste. Our experience indicates that systemic lupus is an important finding after splenectomy in many patients with adequate follow-up examination. (Rabinowitz and Dameshek: *Ann. Int. Med.* 52:1 [Jan.] 1960.)

In any event, the present availability of fresh blood in plastic bags and of the corticosteroids reduces greatly the apparently urgent need for splenectomy in patients with ITP. This operation, never a procedure which could be guaranteed as 100% successful, can be left as a final therapeutic measure if a remission does not develop after a suitable length of time. Carpenter's article states that we have challenged the therapeutic superiority of splenectomy. In a condition as protean as ITP, in which there are many self-limited cases and many others which seem to be self-perpetuating whatever one does, it is indeed high time that splenectomy should be challenged as a completely rational procedure. Greatest attention should be concentrated on pathogenic mechanisms such as the immunological one and on the types of therapy that may influence these functional disturbances. To be sure, the therapeutic measures presently available may not be completely effective, but if a certain number of patients are spared needless splenectomies, such measures are preferable. The statistic of 81% complete remissions after splenectomy and only 38% after the administration of corticosteroids is indeed a striking one, but time and the analysis of more cases will be needed before its significance can be fully evaluated.

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REVIEWS OF LITERATURE

To the Editor:—In the clinical note, "Agranulocytosis Due to Administration of Salicylazosulfapyridine (Azulfidine)," in The Journal, Jan. 16, p. 237, the authors declare, "We are aware of only one other occurrence of agranulocytosis associated with administration of this drug." Just prior to making this statement, they mention a case described by Levy in 1949 (reference 6), while the case to which they refer in their statement is one of which they were informed through a personal communication (reference 7).

A report has been made by Evans and Ford (Studies of Bone Marrow in Immunological Granulocytopenia, *A. M. A. Arch. Int. Med.* 101:244 [Feb.] 1958) of another such case, and there is, in addition to this, a fourth case which has been recorded in the literature. The first case occurred in a patient after he had been taking 4 Gm. of salicylazosulfapyridine daily in divided doses for about two months. At the time of his admission to hospital, the following data were recorded: "Granulocytes were not found in the blood smears. The initial leukocyte count was 1,150, of which 1% were monocytes and 99% were lymphocytes. The platelets and red blood cells appeared normal in the blood smears. The hemoglobin level was 12 Gm. per 100 cc."

In addition to the patient they describe in the above-mentioned report, the authors referred to two other patients in whom severe granulocytopenia was attributed to salicylazosulfapyridine. They cited two articles, the one by Levy (reference 6) and one other by Svartz (reference 1) in the bibliography of The Journal report. I subsequently found that Svartz also reported a case of the same sort.

This information is brought to your attention to insure that the information reported in The Journal is accurate and to point out that medical literature searches sometimes may not be as fruitful as they might otherwise be because the major title of the paper indexed does not significantly or completely reflect its subject content. This latter problem is one I have studied for a number of years.

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CORRESPONDENCE

ANTICOAGULANT THERAPY IN HEPATIC DISEASE

To the Editor:—I have read the paper by Kliesch and associates (*J. A. M. A.* **172**:223 [Jan. 16] 1960) relating to the dangers of anticoagulant therapy in hepatic disease and especially to hemorrhagic complications in the patient receiving long-term anticoagulant therapy who develops an intercurrent acute hepatitis. Within the past year I have encountered two such patients, both middle-aged women who had been placed on long-term anticoagulant therapy for repeated bouts of coronary insufficiency. In one patient there had been accompanying thrombophlebitis with probable pulmonary embolism. As a rule neither patient consumed alcohol. The conditions of both were effectively maintained on anticoagulant therapy for six and four months, respectively, in one with bishydroxycoumarin and the other with phenprocoumon. Frequent checks of the prothrombin time were consistently within the range of 20 to 25 seconds while they were outpatients. Both patients then manifested severe hematuria accompanied by high prothrombin times.

One patient was carefully studied for possible renal lithiasis or other genitourinary disease. None was found. She then was found to have a sulfobromophthalein retention of 23% at 45 minutes. The bleeding ceased two days after she was given intramuscular injections of vitamin K. Her sulfobromophthalein test showed normal results after she was out on a regimen of modified rest, diet, and vitamins. In the other patient the diagnosis of hepatitis was made indirectly. A urinalysis revealed numerous red blood cells per high-power field after she noticed that her urine was dark. Her prothrombin time was 41 seconds. Two days after the intravenous administration of 20 mg. of conjugated estrogens and the administration of 10 mg. of vitamin K_1 by mouth her urine was still dark brown. At that time urinalysis failed to reveal any significant hematuria, but a high titer of urinary urobilinogen with mild jaundice was noted. Thereafter the patient manifested the clinical findings of acute hepatitis.

Accordingly the persistence of urinary discoloration after hematuria has been controlled should alert the clinician to the presence of an intercurrent acute hepatitis. This sequence deserves great attention because of the high incidence of viral hepatitis and the frequency with which this diagnosis is overlooked. It has been my experience in a medical consultation practice that a significant majority of patients, especially women, in whom the diagnosis of subacute or chronic hepatitis ultimately is made do not have clinical jaundice.

In acute bleeding episodes complicating long-term anticoagulant therapy, I have found that the administration of one or several intravenous injections of conjugated estrogens along with temporary cessation of the anticoagulant will completely control the acute bleeding. This then enables the patient to resume use of the anticoagulant without incurring either the risk of a rebound hypercoagulability state associated with the sudden cessation of anticoagulant therapy or the difficulties encountered in reestablishing an effective hypoprothrombinemic range after the administration of vitamin K or vitamin K_1 (Roberts, H. J.: Intravenous and Oral Estrogens in Management of Bleeding Associated with Long-Term Anticoagulant Therapy, to be published).

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TREATMENT OF IDIOPATHIC THROMBOCYTOPENIC PURPURA

To the Editor:—The article by Carpenter and others (*J. A. M. A.* **171**:1911 [Dec. 5] 1959) on the treatment of idiopathic thrombocytopenic purpura (ITP) is worth reading carefully. The apparently striking superiority of splenectomy (81% complete remissions) to corticosteroid therapy (38%) in this series of patients may have to be questioned as further statistics become available. Thus comparison of the results of splenectomy with those obtained by the larger doses of steroids used in patients in the New England Center Hospital would be desirable.

Although the views from the two clinics may seem at first glance to be quite divergent, there are many points of agreement. Aside from the difficulties involved in interpreting carefully culled statistics derived from small numbers of clinical cases, the main lesson that may be drawn from the article is that one should not immediately decide that splenectomy is superior as a therapeutic method for this disease. It is clear from this paper and from one by Hirsch and myself (*A. M. A. Arch. Int. Med.* 88:701 [Dec.] 1951) that acute, self-limited cases occur chiefly after infections and administration of drugs and that a large proporupper abdomen on the right gradually eased. His condition was maintained with an antispasmodic and an antacid given by mouth; since a mixture of milk and cream was not well tolerated, milk alone was given. The patient became depressed and exhibited peculiar mental symptoms characterized by confusion and memory loss. A few days later he showed injection of the sclera and complained of diplopia, photophobia, and marked pain on convergence. Ophthalmologic examination revealed only injection of the scleras. The patient was treated with vitamin B_{12} empirically. Heartburn and abdominal cramps persisted in spite of antacid and antispasmodic medication. In addition, he showed increasing intolerance of the Sippy diet.

Despite incomplete response to the ulcer diet, the patient was discharged, but later had to be readmitted. Because of increased serum calcium content, further investigation was thought necessary to rule out parathyroid pathology or malignant disease before any surgery for the ulcer was undertaken. Skull films revealed marked decalcification, particularly in the parietal bones, and a cystic area was noted in the mandible. Other films of the skeleton showed general decalcification with marked loss of normal trabeculation and thinning of some cortices. A chest film showed a cystic area in 2 ribs plus increased pulmonary markings. Abdominal films suggested nephrocalcinosis. At operation a parathyroid adenoma was found. After surgery minor signs of tetany were controlled by calcium gluconate powder given by mouth. With no further therapy for the peptic ulcer, a barium-meal examination revealed a healed ulcer, and there have been no further ulcer complaints.

The author points out that hyperparathyroidism due to adenoma is a disease of protean manifestations. Its diverse symptomatology is a result of impaired and altered physiology of other organs due to the chemical imbalance. Some of these secondary effects become so pronounced that they overshadow the true nature of the disease. The literature of recent years shows an increased recognition of peptic ulcer in hyperparathyroidism, but confirmation of this association has been hindered by (1) surgical treatment of the ulcer prior to the diagnosis of the underlying hyperparathyroidism and (2) the family history of ulcer tendency in several of the cases reported. The case presented here and others in the literature emphasize the difficulty of diagnosis. The results of tests for calcium, phosphorus, and alkaline phosphatase are often inconclusive. A dislike or intolerance for milk may be significant. Early diagnosis of hyperparathyroidism would seem to depend largely on an awareness of the diversity of symptoms, and a realization that many symptoms stem from the organs or systems secondarily affected by the hyperparathyroidism. The symptoms that may accompany hyperparathyroidism may involve the gastrointestinal tract, the musculoskeletal system, the urinary tract, the cardiovascular system, and the nervous system; in addition, there may be eye symptoms, chills, fever, weight loss, pallor, and headache. The conditions associated with hyperparathyroidism include, in addition to urinary tract disorders, particularly calculi, osteitis fibrosa generalisata, pathological fractures, peptic ulcer, pancreatitis, adenomas of the pituitary or pancreas, anemia, psychosis, hypertension, and hypomagnesemia.

A Case of Congenital Hemolytic Anemia with Hypersplenism: Remission of 24 Years Following Splenectomy and Recurrence Due to an Accessory Spleen Visualized by Thorotrast. R. Lombardo and T. S. Evans. Connecticut Med. 24:17-20 (Jan.) 1960 [New Haven].

One of the reasons for failure of splenectomy to cure the hypersplenic syndrome is the presence of an accessory spleen which is left behind at the original operation. A case of this nature is reported, in which a 24-year remission followed splenectomy. The patient, then a 21-year-old man, was admitted to the Hospital of St. Raphael in New Haven, Conn., complaining of progressive weakness of 3 weeks' duration. "Diffuse dermatitis" and a movable mass in the left upper quadrant were observed. The only laboratory data available were a 60% hemoglobin level, a white blood cell count of 10,200 per cubic millimeter with 73% polymorphonuclear leukocytes and 27% of lymphocytes, and a red blood cell count of 3.9 million per cubic millimeter. A splenectomy was performed; microscopic study of the spleen showed marked congestion, hemosiderosis, dilatation of the sinuses, sclerosis of the vessels, and phagocytosis of red blood cells. The postoperative period was uneventful, and the patient was discharged in good condition.

Fifteen years after the operation the patient sought medical advice because of abdominal pain and weakness of 2 weeks' duration. Hypersplenism secondary to an accessory spleen was suspected, but the patient refused all treatment. He was again admitted to the Hospital of St. Raphael 9 years later, apparently having been well until 3 weeks prior to the admission. Anorexia, fatigue, and watery stools were his main symptoms. The red blood cell count was 4.17 million per cubic millimeter, the white blood cell count, 16,850 per cubic millimeter; and the hemoglobin level, 11.8%. The bone marrow showed erythroid hyperplasia consistent with peripheral blood loss or destruction. X-rays showed a poorly defined reticular infiltration throughout the lung fields. A flat film of the abdomen revealed several calcified, faceted gallstones in the right upper quadrant. After a period of medical treatment, to which he did not respond, the patient was given thorium dioxide (Thorotrast) intravenously, in a dose of 25 cc. on 3 successive

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

The Role of Hypertension in the Progression of Atherosclerosis. J. C. Paterson, J. Mills and C. H. Lockwood. Canad. M. A. J. 82:65-70 (Jan. 9) 1960 [Toronto].

Increased intra-arterial pressure is generally regarded today as an important factor in the acceleration of atherosclerosis. However, except for the well-known atherogenic effects of pulmonary hypertension, the evidence for this acceleration is nearly all of the indirect type. Most of it is concerned with the relationship of hypertension to clinical coronary artery disease, not to coronary atherosclerosis as such, and even with clinical coronary artery disease, inconsistencies are apparent. For example, there are populations in which hypertension is not uncommon, whereas the prevalence of ischemic heart disease is relatively low. Furthermore, hypertensive disease is said to be more prevalent in middle-aged American women than in men, but the opposite is the case for atherosclerotic disease, particularly coronary artery disease.

The authors had an opportunity to investigate these matters in the course of a long-term study on 800 male patients who were permanently confined to hospital. In each of these, in addition to the serial determinations of the serum lipids, blood pressure recordings had usually been made intermittently over many years. Now the authors have been able to compare these blood pressure levels with the amount of arterial lipid deposits in the 184 fatalities in this series. The 184 men who died ranged in age from 50 to 89 years.

The amount of lipid extractable from the arteries of patients with hypertension (systolic or diastolic) was compared with the amount in patients with normotension. Significant relationships between systolic hypertension and the amount of arterial lipid were demonstrated in the coronary, cerebral, and femoral arteries but not in the abdominal aorta. For the diastolic group a significant relationship was shown between this type of hypertension and the amount of lipid in the cerebral arteries, and a borderline relationship in the coronary arteries. Significant relationships between hypertension and the accumulation of lipid in arteries were demonstrated in 7 of 12 separate statistical analyses, and in the remainder a trend in favor of hypertension was demonstrated.

It should be noted particularly that significant relationships between hypertension and the amount of arterial lipid have been found consistently in the vessels that are of the greatest clinical importance—the coronary and cerebral arteries. The mechanism by which hypertension accelerates the atherosclerotic process is discussed, and it is suggested that it lies in the increased tendency of hypertensive patients to rupture intimal capillaries and produce intimal hemorrhages.

Familial Cardiomegaly. E. Voridis and P. Maurice. Arch. mal. coeur 52:1410-1420 (Dec.) 1959 (In French) [Paris].

Observations on 3 siblings with familial cardiomegaly of the type described by Evans are reported. Two of the male patients, 56 and 52 years of age, respectively, are still alive; the third patient, a woman, died suddenly at the age of 56. Electrocardiographic examination showed incomplete blocking of the left branch, as well as atrial and ventricular hypertrophy of the left heart, in all 3 patients. A more or less significant cardiomegaly, predominantly of the left ventricle, was always present on x-ray examination. A genealogical study made among members of 10 families known to have cardiomegaly of the Evans type confirmed the authors' suspicion that in this condition a hereditary factor is predominant.

Peptic Ulcer: A Manifestation of Hyperparathyroidism. E. K. Morse. J. Maine M. A. 51:1-6 (Jan.) 1960 [Portland].

The author presents the history of a man who was hospitalized with severe upper abdominal pain. For 10 to 15 years he had had attacks of indigestion characterized by epigastric distress and heartburn. Examination gave the impression of a penetrating gastric or duodenal ulcer. As there was evidence of sealing, the patient was treated conservatively by gastric suction, sedation, parenteral administration of fluids, and antispasmodic and antibiotic preparations. He showed good response under conservative management; tenderness and spasm of the

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The place of publication of the periodical appears in brackets preceding each abstract.

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and pancreatic function tests may be entirely normal. The findings in these 2 families afflicted with chronic idiopathic jaundice illustrate the variation in expressivity of the metabolic error which is presumed to underlie the disorder. Low orders of involvement occur, which are difficult to recognize clinically and by laboratory study or even by close examination of the liver biopsy specimen.

Familial Chronic Idiopathic Jaundice (Dubin-Sprinz Disease), with a Note on Bromsulphalein Metabolism in This Disease. E. Mandema, W. H. de Fraiture, O. Nieweg and A. Arends. Am. J. Med. 28:42-50 (Jan.) 1960 [New York].

The authors report on a 44-year-old man, a 40-year-old woman, and 3 of the latter's brothers, between the ages of 25 and 35 years, with chronic idiopathic jaundice (Dubin-Sprinz disease), who were admitted to the University Hospital in Groningen, The Netherlands. The father, a brother, and a sister of the 44-year-old man had jaundice of long standing, possibly caused by Dubin-Sprinz disease; none of these family members were studied. The other 4 patients apparently had healthy parents, brothers, and sisters, and 3 children of the patients who were examined did not show any abnormalities. In 2 of the 5 patients cholelithiasis was observed. In 2 patients without cholelithiasis, the gallbladder could be well visualized after intravenous administration of a contrast medium, but only after a delay of 5 hours. After the intravenous injection of 2 to 6 mg. of Bromsulphalein per kilogram of body weight, the Bromsulphalein concentration was estimated in blood samples obtained every 3 to 5 minutes from the fasting patients and from normal contratest persons. Chromatographic studies of Bromsulphalein in the urine and bile of the patients and of contratest persons were also performed. The results of these studies have shown that the uptake of Bromsulphalein by the liver during the first period after the injection is apparently unchanged. Bromsulphalein is conjugated in patients with chronic idiopathic jaundice, as it is in normal persons. The excretion of conjugated Bromsulphalein into the bile is markedly delayed in patients with chronic idiopathic jaundice in comparison with normal persons. This results in reentry of some of the conjugated Bromsulphalein from the liver cells into the blood stream, and excretion of an excess of conjugated Bromsulphalein by the kidneys into the urine.

The findings in these patients gave additional proof of the familial (hereditary) nature of chronic idiopathic jaundice and of the clinically innocuous course of the disease in most patients. The observed abnormalities in the Bromsulphalein metabolism, together with the familial occurrence, may be useful in establishing the correct diagnosis.

SURGERY

Complete Correction of Fallot's Triad in Extracorporeal Circulation in a Pregnant Woman. G. Dubourg, P. Broustet, H. Bricaud and others. Arch. mal. coeur 52:1389-1391 (Dec.) 1959 (In French) [Paris].

The case of a 38-year-old woman, 3 months pregnant, with Fallot's triad, who at the onset of severe decompensation was operated on for complete correction of the cardiopathy, is reported. The operation was performed with open-heart surgery and with the help of extracorporeal circulation. The recovery of the patient and the retention of the fetus point out the compatibility of this operation with pregnancy.

Bronchogenic Carcinoma. A. Ochsner, A. Ochsner Jr., C. H'Doubler and J. Blalock. Dis. Chest 37:1-12 (Jan.) 1960 [Chicago].

Eight hundred seventy-five patients with bronchogenic carcinoma were treated at the Ochsner Clinic in New Orleans between 1942 and 1957. There were 769 men (88%) and 106 women (12%) in this series. The authors believe that the reason for the higher incidence in men is that men smoke more than women. The right lung was involved in 53.4% of the patients, and the left lung in 46.6%. The 2 upper lobes were involved with equal frequency (27%). These lobes are primarily involved in cancer of the lung because it is there that the greatest concentration takes place during the inhalation of smoke. The most frequent form of tumor was epidermoid carcinoma (present in 52% of the patients); undifferentiated tumors were found in 29%, and adenocarcinoma in 19%. The histological type of tumor varies according to the sex, largely because men smoke more than women. Epidermoid tumors, which are largely the result of smoking, occur more frequently in men than in women; in this series, 54% of the men and 33% of the women had epidermoid carcinoma. The diagnosis was established by bronchoscopy in 33% of the patients and by repeated examinations of the sputum in 67%. The sputum was obtained by bronchoscopic aspiration from deep within the bronchi. Bronchoscopy alone was of little value in many cases in which the tumors were located in the upper lobes, because they are not visible through the bronchoscope.

The lung tumor was so far advanced in 330 (34%) of the 875 patients studied that it was considered inoperable. Pneumonectomy was the preferred type in 94% of the 356 resections performed; the remaining patients underwent lobectomy. The over-all survival rate was 6 months in 41% of the patients, one year in 24%, 2 years in 10%, 3 years in 8%, 4 years in 7%, and 5 years in 6.5%. Most of the patients whose lesions were inoperable, or who re-days. A round opacification in the left upper quadrant was noted by flat plate. At operation an accessory spleen weighing 65 Gm. was removed. It was covered with a thick capsule and fat tissue. A biopsy of the liver showed portal cirrhosis. The patient had a continuous downhill course, with ascites, paralytic ileus, and electrolyte imbalance. Death occurred on the 15th postoperative day. A study of the patient's family revealed evidence of congenital hemolytic anemia in a son, and suggestive evidence was found in other members of the family group.

Transformation of Chronic Myeloid into Acute Leukemia. J. Bernard, M. Séligmann and R. Kvicala. Rev. franç. étud. clin. et biol. 4:1024-1035 (Dec.) 1959 (In French) [Paris].

The authors report on 67 men and 48 women with chronic granulocytic (myeloid) leukemia, who were observed in the St. Louis Hospital in Paris between 1953 and 1959. Of the 115 patients, a transformation of chronic granulocytic leukemia into acute leukemia occurred in 33, 28 of whom were studied in detail. Forty-six patients died, and among them were the 33 (72%) in whom the transformation into acute leukemia had occurred. Such an acute transformation is, therefore, the commonest cause of death among patients with chronic granulocytic leukemia. The period of time within which such a transformation occurs may vary from 2 months to 5 years after the onset of leukemia, and there does not seem to be any definite correlation with the preceding treatment. A profound asthenia and fever are the usual clinical manifestations which may reveal the acute transformation. The first, and possibly for a considerable time the only, clinical sign may be an adenopathy. Sometimes the transformation may only be apparent from examination of the peripheral blood and bone marrow.

Hematological studies revealed that the predominant cell forms are not always classic myeloblasts, but sometimes premyelocytes and sometimes undifferentiated hemocytoblasts. Myelocytes and metamyelocytes may be present with blast cells, but usually the myelocytes and metamyelocytes have disappeared, and there may be a secondary appearance of the "leukemic hiatus." Basophilia appears less frequently than is usually assumed. Anemia and thrombopenia are common but do not occur without exception.

Busulfan (Myleran), the drug of choice for the treatment of chronic granulocytic leukemia, proved ineffective after the occurrence of transformation into acute leukemia. Very large doses of cortisone (listed by the authors as 1 to 3 Gm. given daily by intramuscular route) or prednisone (200 to 400 mg.) or mercaptopurine (2.5 mg. per kilogram of body weight daily), either separately or in combination, may cause partial or complete remissions. In the case of a complete remission, an eventual relapse is not necessarily associated with blast cells and may occur in a chronic granulocytic form. Two patients with this latter form of relapse were treated successfully with busulfan, but several weeks later a renewed increase of leukocytoblasts caused the death of the patients.

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Chronic Idiopathic Jaundice: A Study of Two Afflicted Families. R. L. Wolf, M. Pizette, A. Richman and others. Am. J. Med. 28:32-41 (Jan.) 1960 [New York].

The authors report on 2 Puerto Rican families in which the diagnosis of chronic idiopathic jaundice was established by liver biopsy in several members of both families. The first family was comprised of both parents and 10 of their children; of the 8 family members with the disease (the mother, 3 male and 4 female siblings), jaundice occurred in 2 in early childhood, and in one each at the ages of 24 and 33 years, respectively; the remaining members were unaware of the presence of jaundice. All the members studied were asymptomatic except 2; one had abdominal pain, nausea, vomiting, and weakness, and the other had abdominal distress after eating fatty foods. The second family consisted of both parents and their 6 children. Of the 3 known siblings with the disease (2 females and 1 male), only one reported jaundice since childhood. This patient had had mild abdominal distress for one year. All the remaining members investigated were asymptomatic, and there was no family history of jaundice or symptoms referable to the disease. Eight members (5 of the first family and 3 of the second family) were found to have varying amounts of hepatic cellular pigment on liver biopsy. Ten members were found to have hyperbilirubinemia.

The microscopic appearance of the liver of 2 members of the afflicted families showed the fully developed picture of chronic idiopathic jaundice. In 4 members a mild degree of pigment deposition was found, and in 2 a borderline increase of the same pigment was noted. In one anicteric member the amount and distribution of pigment varied only slightly from the normal. It would, therefore, appear that some members of families with chronic idiopathic jaundice may have only a borderline increase in pigment. The conspicuous hepatic pigment shown in chronic idiopathic jaundice results from the accumulation of a pigment present in small amount in the centrolobular zone of a normal liver. The results of Bromsulphalein retention tests and oral cholecystography are not necessarily abnormal in persons in whom accumulation of the pigment characteristic of chronic idiopathic jaundice is not greatly in excess, even in the presence of jaundice. Hepatic no worthwhile conclusions can be drawn from their earlier cases. The bypass methods employed initially often did not suffice for proper correction of the lesion. While brilliant results were obtained in some individual cases, the over-all results during the early period would be misleading with regard to present possibilities. Therefore, the authors have tabulated the results of corrective surgery for aortic regurgitation only in their last 25 consecutive patients. The results, as far as the valvular correction was concerned, were excellent in 15 patients, good in 6, fair in 2, and unsatisfactory in 2. A few of those with excellent or good valvular results died within a few days, or weeks, after the operation as the result of anoxic enncephalopathy or nephrosis. It is urged that patients be operated on before they reach a terminal or preterminal state.

A Study of Recurrent Pulmonary Embolism. J. F. Schauble, W. G. Anlyan, H. L. Deaton and others. A. M. A. Arch. Surg. 80:105-112 (Jan.) 1960 [Chicago].

This paper presents a clinical analysis of recurrent pulmonary embolism as seen at the Duke University Medical Center, Durham, N. C., since 1950. Corollary physiological studies in patients with thromboembolic disease undergoing vena caval ligation are also outlined. Among the 416 patients with pulmonary embolism seen since 1950, there were 109 who had definite clinical evidence of recurrence, as judged by various combinations of findings, including acute pleuritic chest pain, dyspnea, hemoptysis, friction rub, fever, tachycardia, and electrocardiographic and x-ray changes compatible with pulmonary embolism and right heart failure. Although the conclusive diagnosis of pulmonary embolism can be made only by postmortem examination, the patients in this series had overwhelming clinical evidence, questionable cases being excluded. The majority of recurrences occurred in patients in whom the initial embolus was not recognized, and no adequate treatment was given.

Recurrent embolism occurred in 12 patients while on heparin therapy and in 24 patients on coumarin therapy. Recurrence after the discontinuance of anticoagulant therapy was noted in 28 patients and led to consideration of vena caval ligation. After vena caval ligation only 1 of the 21 patients followed had a subsequent pulmonary embolus. This may not represent a true failure of vena caval ligation, since the patient had evidence of venous thrombosis in both arms at the time of the recurrent embolus.

Pressure studies performed on patients undergoing vena caval ligation indicated that 60% of them showed no change in venous pressure after ligation, presumably because the equivalent of the ligation had already been produced by the thrombotic occlusion. The syndrome of recurrent silent pulmonary emboli in the absence of clinical evidence of venous thrombosis in the extremities may constitute a difficult problem in diagnosis. Progressive enlargement of the pulmonary arterial outlines at the hili and the gradual disappearance of peripheral pulmonary arterial tributaries are highly suggestive of this syndrome.

Subisthmic Aortic Stenosis and Occlusive Disease. G. C. Morris Jr., M. E. De Bakey, D. A. Cooley and E. S. Crawford. A. M. A. Arch. Surg. 80:87-104 (Jan.) 1960 [Chicago].

Congenital coarctation of the aorta generally involves the distal aortic arch or isthmus in all but 2% of the cases. With increasing experience in the surgical management of isthmic coarctation, greater interest has been aroused in the relatively rare and more challenging subisthmic form of aortic stenosis. Although the clinical picture in both of these forms of coarctation is often quite similar, the surgical approach required for each of them may be different. While routine aortography is not necessary for all cases of coarctation, it is essential in the subisthmic form of the disease. In a few instances, it has revealed a second unsuspected occlusive lesion.

Analysis of 21 cases observed by the authors, as well as a review of the isolated literature reports, suggests the presence of certain distinguishing clinical features of subisthmic coarctation. Clinical and morphologic characteristics provide a division of these subisthmic aortic occlusive lesions into 3 levels of involvement, namely, lower descending thoracic aorta, upper abdominal aorta, and lower abdominal aorta above the bifurcation. There were 4 patients in the first group with subisthmic coarctation of the lower thoracic aorta. The differential diagnostic features of subisthmic coarctation are based on the minimal development of collateral circulation. The level and extent of the occlusive process are revealed by aortography. Resection with graft replacement is the treatment of choice.

In 4 instances in the second group an obstruent process involved the upper abdominal aorta. Hypertension was severer in this group. The bypass principle of surgical treatment is generally most applicable in these cases. The third group was composed of patients with obstruent processes in the lower abdominal aorta proximal to the bifurcation. The obstructing process was produced by intimal thickening in 4 young adults. In 12 other patients, whose ages were in the 4th and 5th decades, thrombo-obliterative alterations resulting from arteriosclerosis produced the obstruction. Endarterectomy constituted the primary bases of surgical correction for segmental occlusive processes of the lower abdominal aorta above the bifurcation.

fused the operation, were given some type of palliative therapy; 60% of them were alive at the end of 6 months, 40% at the end of one year, 20% after 2 years, but none at the end of 3 years. The 5-year survival rate was 6.2% in men and 10% in women. The type of lesion was an important prognostic factor. The 5-year survival rate was 21% in the patients with epidermoid carcinoma, 11% in those with undifferentiated lesions, and 7% in those with adenocarcinoma. The authors believe that the tremendous increase in the rate of cancer of the lung is related to cigarette smoking, and they advise that all smokers should have a chest x-ray film made every 6 months in order to diagnose symptomless pulmonary lesions before metastases occur.

Diagnosis of Bronchogenic Carcinoma: An Evaluation of Pulmonary Cytology, Bronchoscopy and Scalene Lymph Node Biopsy. W. O. Umiker. Dis. Chest 37:82-90 (Jan.) 1960 [Chicago].

The records of 100 patients who had histologically confirmed lung cancer were analyzed. There were twice as many neoplasms of the upper lobes as of the lower, and 9 tumors either extended into both upper and lower lobes or were confined to main-stem bronchi. Eighty-four patients underwent bronchoscopic examination, including aspiration of bronchial secretions or bronchial washings for cytological examination. Four hundred forty sputum specimens were examined cytologically. Anterior scalene lymph node biopsy was attempted in 78 patients, with a mean number of 4.5 nodes per specimen.

The combined cytological studies of sputum, bronchial secretions, and pleural fluid gave more positive results (76%) than did bronchoscopy and lymph node biopsy combined (60%). More than 40% of the patients who underwent thoracotomy had positive cytological smears as the only preoperative confirmation of the clinical diagnosis. Sixty-three of the 100 patients had positive smears of sputum, and 9 had smears interpreted as suspicious for malignant cells. Although the highest accuracy for sputum examination was obtained in the diagnosis of carcinomas in main-stem bronchi or in the lower lobes, more than half of those in the upper lobes exfoliated detectable malignant cells. Bronchoscopic examination yielded 32 positive bronchial biopsies, 6 visible tumors which could not be subjected to biopsy, and 9 negative visual findings with positive bronchial washings. The addition of cytological examination of bronchial washings increased the accuracy of bronchoscopy in diagnosing upper lobe lesions from 22 to 38%, and permitted the diagnosis of 5 of the peripheral tumors, none of which was visible through the bronchoscope. Scalene lymph node biopsy was the least sensitive diagnostic modality; in only 2 instances did it provide microscopic evidence of malignancy. Its value, when positive, is that it provides not only microscopic confirmation of the diagnosis but also a criterion of inoperability.

Surgical Correction of Aortic Regurgitation. C. P. Bailey, J. Zimmerman, G. Blanco and C. F. Sparger. A. M. A. Arch. Surg. 80:16-30 (Jan.) 1960 [Chicago].

The authors review the development of corrective surgery for aortic regurgitation, pointing out that prior to the advent of open-heart techniques efforts to diminish the cross-sectional area of the "dilated" aortic root by a circumclusion technique were generally unsuccessful. They also note that the introduction of autogenous grafts of pericardium (either free or pedicled) into the supravalvular portion of the aorta, to impose a type of "flap" or "ball-valve" action upon the incompetent structure, was without notable success.

Discussing the development of the open approach to the aortic valve, the authors point out that Lillehei's direct-vision approach in aortic stenosis, in which total bodily perfusion was used with 2 pumps and a DeWall type of oxygenator, was reinforced by support of the myocardium with retrograde perfusion via the coronary sinus, as suggested by Blanco and Adam. This approach was the first method used at their clinic for the correction of aortic regurgitation, but its deficiencies in providing myocardial nutrition soon became manifest. Glowing reports as to the value of elective cardiac arrest in open-cardiac surgery next led them to try potassium citrate and acetylcholine for open surgery upon the aortic valve. Unhappily, many of these arrested hearts proved recalcitrant to resuscitative measures. Finally in April, 1958, they resorted to direct antegrade perfusion of the coronary arteries with oxygenated blood by ostial cannulation. This method has worked well and, with minor technical modifications, is felt to be the *sine qua non* for circulatory recovery after prolonged open or direct-vision surgery in the region of the aortic valve.

Various techniques of valvular correction are described and illustrated in diagrams. Since, however, the pathological variations which are capable of causing aortic insufficiency are many, may be rather complex, and often are found in combination, it usually is not possible to formulate in advance an appropriate operative plan. However, once the lesion has been inspected, one technique, or a suitable combination of several corrective techniques, may be applied in accordance with the requirements of the individual case.

Although the authors have carried out various types of direct-vision "repair" of the incompetent aortic valve in more than 75 patients, they feel that vaginal smears. The incidence of spontaneous abortion is about 10% of all recognized pregnancies; abortion threatens probably in about 15% of pregnancies. About 50 to 60% of threatened abortions go on to abort. Such figures are admittedly very crude, and there is gross discrepancy between (*a*) the pessimistic figures of the pathologists, who study aborted material and believe that more than half of threatened abortions are so defective as to make miscarriage inevitable, and (*b*) the findings of the obstetricians, who try to prevent threatened abortion and report about 80% success in doing so. However, if threatened abortions go on to term, about 4 or 5% of the infants delivered show anomalies.

Vitamin E (alpha-tocopherol) is as effective as any reported therapeutic agent in the management of threatening abortion, literature reports suggesting an 80% salvage rate. In the past 20 years, however, the interest of obstetricians in vitamin E had subsided, chiefly because of the use of estrogenic substances, but now that confidence in the use of estrogen for abortion is at a low ebb, the author feels that the time has come to reevaluate vitamin E. He has had a rare experience in this field in that for the past 25 years he has prescribed vitamin E routinely for each registered private obstetric patient from the beginning to the end of pregnancy. In a total of 4,141 pregnancies so treated, the incidence of abortion and miscarriage was 3%. Perhaps the actual corrected figure for spontaneous abortion should be 5%, which is about half the usual figure quoted by investigators in this field. There were 139 threatened abortions and 93 threatened miscarriages. The salvage rate was, respectively, 76 and 96%, and the incidence of anomalies was, respectively, 6 and 4%. Surely these 13 babies, only 7 of whom lived, were not too high a price to pay for the lives of 182 normal children.

The Incidence and Character of Staphylococcus Aureus from Nose and Rectum of Obstetric Patients. J. C. Hancock Jr., A. D. Dulaney and M. G. Caldwell. South. M. J. 52:1525-1529 (Dec.) 1959 [Birmingham, Ala.].

Five hundred eighty-one cultures of staphylococci were isolated from the nose and the rectum of 50 obstetric patients (primiparas and secundiparas) on admission and at discharge from the city of Memphis (Tenn.) Hospitals. Three colonies of staphylococci were selected from each positive Petri plate for study. Of the 581 cultures of staphylococci, 134 included Staphylococcus pyogenes var. aureus and 447, Staph. pyogenes var. albus. Of the 50 patients, 18 yielded Staph. aureus on admission, while 3 days later at discharge 20 carried those organisms. Thirty of the 50 patients carried Staph. aureus at some time, either on admission or at discharge, or at both times. Thirty-two patients entered the hospital free of Staph. aureus; of these, 12 acquired the organisms during the 3-day stay. Of the 18 patients entering with Staph. aureus, 10 lost the organisms. Eight of the 12 patients who acquired Staph. aureus during hospitalization yielded organisms of phage group 3 or type 80/81. Thus, 80% of the staphylococcic organisms acquired during the 3-day hospital stay belonged to phage types resistant to antibiotics.

Treatment with antibiotics had no significant effect on the acquisition of Staph. aureus. The hospital chemotherapeutic regimen consisted of a combination of penicillin, streptomycin, and sulfisoxazole (Gantrisin). Of 7 patients who acquired group 3 Staph. aureus, only 1 received antibiotics. Of the 10 patients losing Staph. aureus, 5 received antibiotics. It would seem that the danger of acquiring antibiotic-resistant organisms was not increased by the chemotherapeutic regimen carried out in this group of patients. However, there was a danger to all the patients in the hospital environment of acquiring Staph. aureus. Patterns of antibiotic sensitivity were determined on Staph. albus cultures from the first 24 patients. Twenty-two of these yielded penicillin-resistant Staph. albus. In 8 of the 30 patients who carried Staph. aureus, the organisms were isolated from both the nose and the rectum. In 6 instances these nasal and rectal organisms were of the same type. Upon the patients' admission, the distribution of the organisms was very similar, and there was no significant difference in antibiotic sensitivity between the 2 categories. These facts would seem to bear out the idea that a state of "fecal carrier" of epidemic Staph. aureus may possibly exist.

Primary Carcinoma of the Fallopian Tube with Report of 12 New Cases. G. E. Hayden and E. L. Potter. Am. J. Obst. & Gynec. 79:24-31 (Jan.) 1960 [St. Louis].

The authors review observations on 12 patients with primary carcinoma of the fallopian tube, including one case of carcinoma in situ. The cases were diagnosed at the Chicago Lying-in Hospital between 1931 and 1957, constituting 1.1% among 1,087 primary carcinomas of the genital tract. The lesions met the following criteria: 1. The main tumor was within the tube. 2. The mucosa was replaced by an adenocarcinoma which showed the histological characteristics of the endosalpinx. Eleven of the 12 lesions were unilateral, and 1 was bilateral.

All 12 patients were married, but 6 of them had had no term pregnancies. In this connection it is pointed out that many authors stress the frequent association of sterility with primary carcinoma of the tube. All 6 of the nulliparous women had evidence of chronic salpingitis, which most likely was the major factor in the infertility and possibly even

NEUROLOGY & PSYCHIATRY

On the Occurrence and Significance of Provoking Factors in Poliomyelitis. A. Tschuschner. Arch. Kinderh. 161:43-60 (no. 1) 1959 (In German) [Stuttgart, Germany].

The author reports on 79 patients (children and adults) with poliomyelitis, who were studied in the pediatric clinic of the City of Regensburg, Germany, in 1956-1957. The relatively small number of patients had the advantage that a reliable history was obtained from almost every patient and that evaluation and critical selection were warranted. The clinical observations showed the presence of provoking and localizing factors in every second patient. In 2 brothers, a 2-year-old boy and a 4½-year-old boy, combined pertussis-diphtheria-scarlet fever vaccine injections into the thigh preceded shortly the onset of poliomyelitis, which was associated with paresis of the lower extremity. The paresis persisted after one year. The course of the disease in these patients justifies the conclusion that even minor stimuli resulting from intramuscular, but also subcutaneous, injections elicit function of the neurogenic-hormonal apparatus and herewith the infectious event. Tonsillectomy proved to be an eliciting factor in 2 patients. Suppurative sore throat played the part of an injurious agent in the course of the poliomyelitis in 5 patients; a retrotonsillar abscess, in 1; and chronic tonsillitis, in 1. In 3 additional patients combined tonsillar hypertrophy and dental fistula constituted the damaging factor in the course of the disease.

Appendicitis, conjunctivitis, and otitis were predisposing factors in one patient each who had poliomyelitis. In 2 patients bronchopneumonia, which preceded the onset of poliomyelitis, was considered to be the damaging factor. Chickenpox and German measles presented damaging factors in 1 patient each; gastroenteritis, in 3 patients; and dislocation of the hip joint, in 1. Occupational overexertion of the muscle groups of the arm predisposed the upper extremities to paresis in one patient. Contusion of the head, resulting from a fall on the stairs preceding the poliomyelitis, was a damaging factor in one patient. Exogenous circulatory stimulation by intensive sun irradiation elicited the onset of the disease in a 5-year-old fair girl. In 3 patients a preceding voyage and in 1 patient a preceding change of residence had an unfavorable influence on the course of poliomyelitis. Bulbar poliomyelitis in a woman in the 8th month of pregnancy resulted within 3 days in the patient's death. The clinical picture of the disease is most severe in the last trimester of pregnancy.

The author cautions against underrating the provoking and localizing factors in poliomyelitis. These predisposing factors should influence the prophylactic measures to a greater extent than has been the case up to now. Little attention has been paid previously to the deleterious effects of vaccinations and injections and to the chronic recurrent tonsillitis, which were quite impressive as eliciting factors in this series. With the increasing administration of cortisone and its derivatives, a similar damaging influence on the course of poliomyelitis is feared, if this form of therapy is employed during the critical phase, since this is in analogy to the effects of physical exertion entailing stress situations. Tonsillectomies should be performed only after completion of a series of injections with poliomyelitis vaccine. Pregnant women, with their higher susceptibility to poliomyelitis, should take advantage of the rule to stay in bed until the temperature has returned to normal, when they are suffering from influenza during an epidemic poliomyelitis season.

Aseptic Encephalitis: II. Follow-up of 40 Surviving Patients. P. Kildeberg. Ugesk. laeger 121:2001-2004 (Dec. 17) 1959 (In Danish) [Copenhagen].

Of 51 patients with acute aseptic encephalitis admitted to the County and City Hospital in Odense, Denmark, in 1948-1958, 35 had primary encephalitis; 11, measles encephalitis; and 2, varicella encephalitis, while 3 had rubella encephalitis, vaccination encephalitis, and otogenic encephalitis respectively. Ten patients died in the acute stage, and one died afterward. The 40 surviving patients were followed up for an everage of 4½ years after discharge, and none for less than half a year after discharge. Of the 27 patients with primary encephalitis who survived the acute stage, 15 were free from symptoms, 9 were only moderately handicapped, but 3 were severely handicapped. Of the 9 survivors of measles encephalitis, 4 were mentally retarded, and 1 had a spastic paraparesis. Remission was complete in the 2 cases of varicella encephalitis. There was moderate impairment of hearing in the patient who had rubella encephalitis, and some mental retardation and incoordination of finger movements in the one who had otogenic encephalitis.

GYNECOLOGY & OBSTETRICS

Should Spontaneous Abortion be Prevented? Vitamin E in Its Management. E. V. Shute. Canad. M. A. J. 82:72-76 (Jan. 9) 1960 [Toronto].

On the basis of literature reports and his own experiences, the author comments on the following questions: Can abortion be prevented? Should it be prevented? What has vitamin E to offer in its prevention? Spontaneous abortion may be anticipated in a large number of pregnant patients who have low outputs of chorionic gonadotropin or pregnanediol, or defective cervical mucus patterns or beam is well adapted to treatment of lesions which are unilateral in location and relatively subsurface in depth. Neoplasms of the head and neck fall into this category. Parotid tumors, tumors of the tonsillar fossa, of the maxillary sinuses, of the tongue, of the buccal mucosa and the gingival margin, or tumors involving a pyriform sinus are examples of types suitable for treatment with the betatron electron beam. Treatment can be confined to a single side of the oral cavity or pharynx. Homogeneous dosage is placed throughout the tumor-bearing area, including in most instances the primary routes of lymphatic dissemination. Patients were selected for treatment with the betatron electron beam, because their conditions were advanced or hopeless as far as treatment by any other means was concerned. It is remarkable that some have survived. Of 8 patients with squamous-cell carcinoma of the tonsillar fossa, one is alive after 3 years; of 4 with parotid adenocarcinoma, one is alive; of 4 with squamous-cell cancer of the vocal cords, 3 are alive. The shorter follow-up period of the more recently treated, unselected patients suggests that results will be quite favorable when compared with alternate therapeutic methods.

Rotational Cobalt 60 Teletherapy of Vesicle Cancer. H. H. Browne and R. T. Ogden. Am. J. Roentgenol. 83:107-115 (Jan.) 1960 [Springfield, Ill.].

The authors report on 55 patients with primary carcinoma of the bladder, who received treatment with radiocobalt (Co^{60}) at the Hartford (Conn.) Hospital between December, 1954, and January, 1958. The results were compared with those obtained from a comparable group of 45 patients who received surgical treatment under the same circumstances and over the same period of time. Both groups were followed up for from 1 to 4 years. The degree of tumor involvement was divided into 4 main groups: Stage A-B (group 1) included carcinoma in situ, with extension of the tumor into the mucosa and into the muscle of the bladder wall; stage C (group 2) included extension of the disease into the perivesicular fat or the prostatic urethra; stage D (group 3) signified disease within the lymph nodes of the pelvis; and group 4 comprised patients with inoperable condition.

Forty-seven of the 55 patients received the same type of therapy, consisting of irradiation through either 10-by-10 or 10-by-15-cm. ports at tumor depth centered over the bladder and with a daily dose of 200 r over a 5-to-6-week period, accumulating a total dose of between 5,000 and 6,000 r. Five of the 47 patients received more than 6,000 r, and the average total dose in this small group was 8,000 r. The remaining 8 patients received less than 5,000 r, with an average total dose of 4,010 r and a minimum of 3,800 r. Ten of the 55 patients had stage A-B carcinoma, and 4 of these had advanced lesions from the histological point of view.

Survival rates among the irradiated patients were superior to those among the surgically treated patients. Twenty-one of the 55 patients are living. All 10 patients with stage A-B lesions are well and show no evidence of recurrences. Five of 8 patients who were irradiated and who had stage C lesions are living without disease. Four of 23 patients who had stage D lesions are living; 2 are living with disease, and 2 are clinically free of disease. Two of 14 patients whose lesions were inoperable are living with disease after 1½ and 2½ years respectively. Of the 45 patients who received surgical treatment, 39 had stage A-B lesions. Twenty-eight of these are presently living—a survival rate of 72% as compared with 100% among the irradiated patients. All the patients in the surgical groups with stage C and stage D lesions and those whose lesions were inoperable have died. It is emphasized that the value of palliation, aside from end-results and comparative figures, cannot be overlooked as an important factor in alleviating symptoms in many of these patients, even though a cure may not be obtained. This in itself is a worthwhile result, since palliation with this therapy has been more satisfactory and complete than with conventional roentgenotherapy.

Clinical Evaluation of Radioactive Chrome Phosphate in the Control of Malignant Pleural and Ascitic Effusions. C. R. Perryman, E. J. Pavsek and J. D. McAllister. Radiology 73:865-870 (Dec.) 1959 [Syracuse, N. Y.].

A dose of 5 mc. of radioactive chrome phosphate was instilled during thoracentesis on 60 patients with malignant effusions, 38 of whom had the pleural and 22 the ascitic variety of the condition. Excellent results were obtained in 12 patients with pleural effusions and in 4 patients with ascitic effusions. Fair results were obtained in 7 patients with pleural effusions and in 6 patients with ascitic effusions. Results were considered excellent if no additional thoracentesis was necessary for at least 4 months; they were considered fair if there was no necessity for further thoracentesis for 2 to 4 months. The requirement of 1 or 2 additional thoracenteses during the latent period in which the radiation reaction had been developing was not considered a poor result, because the patients may have gone on to a long period of improvement. In this series, 50% of the patients with pleural effusions and 45% of those with ascitic effusions are known to have benefited from the treatment. The remainder either died, had poor results, or were unavailable for follow-up.

It seems that radioactive chrome phosphate is the agent of choice in the treatment of malignant effusions, in preference to radioactive colloidal gold (Au^{198}) and radioyttrium (Y^{90}). A dose of 10 mc. of radioactive chrome phosphate should be used in the abdomen, and one of 5 to 8 mc. in the chest.

a predisposing factor in the development of carcinoma. The diagnosis was never made before operation. The most constant finding on examination was a pelvic or adnexal mass. In 6 of the 12 patients the initial complaint was vaginal bleeding. Six of the patients were postmenopausal, and in 4 of these the initial complaint was vaginal bleeding.

The treatment of choice is total hysterectomy with wide excision of the adnexa. Postoperative irradiation has been recommended, but in this series its value could not be demonstrated. The corrected 5-year survival rate was 27%.

RADIOLOGY

Pyelography in Renal Disease with Hypertension: Correlation Between Pyelographic Findings and Differential Renal Function Studies. L. F. Squire and J. U. Schlegel. Radiology 73:849-864 (Dec.) 1959 [Syracuse, N. Y.].

The authors studied the relative value of pyelographic findings, aortography, and differential renal function studies in 17 patients with hypertension to determine possible renal relation of the disease and the feasibility of the subsequent surgical correction. The intravenous pyelographic findings were no index to the existence of unilateral kidney disease in 9 patients; however, they revealed various morphologic changes which helped to identify the responsible kidney, although the density of the opaque medium was about the same on both sides in 7 patients. The pyelograms were normal in one patient in spite of bilateral depression of function. Aortographic studies, which were carried out on 8 patients, were helpful in indicating the responsible kidney in 7 patients and were equivocal in 1. Differential renal function studies were very valuable in delineating the salvageable patients. They showed which patients had inoperable disease because of bilateral depression of function; they demonstrated in some patients the unilateral disease and the degree of compensation on the contralateral side.

Hypertension related to unilateral renal disease was proved in 6 patients. Nephrectomy, aimed at relief of hypertension, effected a cure in 5 patients. The 6th patient was also cured, but after arterial surgery (shunt graft) for correction of an aneurysm and by performing nephropexy. Nephrectomy failed in 2 patients, who remained hypertensive postoperatively. Both these patients had a long history of hypertension (11 and 12 years respectively). Hypertension attributable to unilateral renal disease is curable in selected patients, provided that nephrectomy or reconstructive arterial surgery is undertaken soon. Unrecognized bilateral disease or fixed hypertension of several years' duration resulting in generalized arteriolar changes is responsible for failure of surgical correction. The intravenous pyelogram is not helpful in indicating a responsible kidney in the absence of morphologic changes. The pyelographic findings, blood chemistry, urine, and conventional renal function studies are often normal in patients with renal ischemia due to some type of arterial obstruction. The radiologist, in reporting a pyelogram as normal, may inadvertently imply the presence of equal function on both sides, and thus reassure the referring physician in abandoning further function studies on the truly salvageable patient. In the absence of contraindications, aortography should be performed on hypertensive patients, along with differential renal function tests, with catheters in both ureters and simultaneous measurement of inulin clearance (glomerular filtration rate), volume in cubic centimeters per minute, and *p*-aminohippuric acid clearance (renal plasma flow).

Therapy in Cancer of the Head and Neck with the Betatron Electron Beam. D. J. Lochman. Am. J. Surg. 98:847-850 (Dec.) 1959 [New York].

The betatron is capable of producing 2 beams, one a beam of high-energy roentgen rays and the other a beam of high-energy electrons. The high-energy roentgen-ray beam has little advantage over the so-called supervoltage roentgen rays in clinical application, and this paper is concerned with the beam of high-energy electrons. The energy distribution in the electron beam is unique, the nearest comparable to it being from an ideal interstitial implant of radium. Although there is no qualitative difference in biological effect between roentgen rays and the electron beam, there are differences in the clinical effect. The following characteristics of the electron beam are mentioned: 1. There is nearly equal dosage throughout most of the range of penetration, and a rather rapid drop in dosage beyond this range. 2. Surface reaction is not a limiting problem as it is with roentgen rays. While the skin is not spared, as would be the case with supervoltage radiation, it need not be overdosed in order to achieve adequate dosage in the deeper tissues. 3. Bone intervening between the source of the beam and the tumor does not cause underdosage of the tumorous tissue beyond; rather, the ultimate depth of penetration of the electron beam is reduced. The increase of absorption in bone over that in soft tissue is less than with conventional roentgen rays, although more than with supervoltage radiation. 4. Depth of penetration can be varied by varying the energy of the beam.

After an initial period of variation in the factors of dosage and time, a standardized technique evolved, based on a tentative optimum dose of 8,600 r in 6 to 8 weeks' total time. All treatments referred to were given with approximately this time-dose relationship. Except for laryngeal fields of about 5 cm. in diameter, field sizes varied between 8 by 9 cm. and 11 by 11 cm. The electron

This study is a contribution to the theory that pyloric antrum functions as an endocrine organ. Its hormone, gastrin, mediates the gastric phase of gastric secretion. The antrum produces gastrin in response to either, or both, chemical (dilute alcohol, crude liver extracts) or mechanical stimulus. Lowering the pH will completely inhibit the gastrin mechanism for either type of stimulus. The critical pH is within an extremely narrow range and is approximately 1.5. This pH is regularly achieved in the normal postprandial stomach. It is theorized that the acid secreted by the stomach in response to the ingested meal reaches a concentration which eventually serves to terminate the gastric phase of gastric secretion.

The Role of the Gastric Antrum in Experimental Ulceration and Regulation of Gastric Secretion. D. State. Gastroenterology 38:15-20 (Jan.) 1960 [Baltimore].

The author studied the role of the antrum in experimentally induced peptic ulceration after the administration of histamine in beeswax to 3 groups of healthy mongrel dogs with small (50%) gastric resection. The results indicated that, when the antrum was left in continuity with a residual gastric pouch, it afforded better protection against histamine-induced "peptic" ulceration than did the Billroth I and II operations. In another set of experimentations, a segmental resection of 50% of the acid-secreting mucosa was performed, and the antrum was either retained or replaced by an equal length of segment of the transverse colon or the jejunum. It was observed that segments of jejunum and transverse colon did not afford the same type of protection as did the antrum. In a third set of experiments on mongrel dogs, it was observed that after the removal of the antrum, even though the amount of acid-secreting mucosa remained unaltered, the incidence of ulceration increased markedly.

Physiological studies were conducted in another series of healthy mongrel dogs to observe the effect of the antrum on the cephalic and gastric phases of gastric secretion. The findings indicated that the antrum was able to reduce gastric secretion when the pH of the contents in contact with the antral mucosa was lowered below pH 1.2. Acidification of antral contents to this degree apparently was able to decrease the cephalic and gastric phases of gastric secretion. The retention of the antrum in operations for duodenal ulcer has several clinical advantages: 1. It eliminates the problem of dealing with a badly scarred duodenum. 2. In the standard Billroth I or II operation, after resection of 75% of the acid-secreting mucosa, the patient is left with only a 25% gastric remnant, whereas after segmental resection of the same amount of gastric mucosa, the patient is left with 40 or 45% of his stomach. A prolonged period of observation is necessary before final evaluation of the efficacy of the segmental resection can be made.

Further Observations on the Mechanism of Ulcer Pain. E. C. Texter Jr., G. R. Vantrappen, H. P. Lazar and others. Ann. Int. Med. 51:1275-1294 (Dec.) 1959 [Lancaster, Pa.].

The authors describe experimental studies, carried out in the course of 8 years on more than 500 patients, to investigate the mechanism of ulcer distress. They studied (1) the effect of intragastric administration of 200 ml. of 0.1 *N* hydrochloric acid on ulcer pain; (2) the fluoroscopic and roentgenographic alterations after the administration of acid-barium; (3) the intraluminal pressures of stomach and duodenum in normal subjects, in patients without ulcer pain, and in patients with ulcer pain; (4) the correlation of the intraluminal pressure changes with the fluorocinematographic appearance of the stomach and duodenum; and (5) the basal gastric secretion and gastric acidity during ulcer pain.

The intragastric administration of hydrochloric acid or of acid-barium was followed by the continuation of spontaneous pain or the induction of ulcer pain in 54 of 155 tests. The gastric acidity was measured initially, prior to and 30 minutes after instilling hydrochloric acid, and 30 minutes after the administration of acid-barium. The initial values did not differ, although the same amount of instilled acid resulted in higher acid values 30 minutes later in patients in whom ulcer pain developed, suggesting delayed evacuation of the instilled acid in this group. Ulcer pain was accompanied by a significant increase in motility, as measured by intraluminal pressure wave activity synchronous with the duration of the ulcer pain. A significant delay in gastric evacuation accompanied the ulcer pain, despite the hypermotility of the antrum. These findings were interpreted as indicative of dyssynergia of the antral-pyloroduodenal evacuation mechanism as the result of increased resistance at the pyloric sphincter. In most instances, relief of pain occurred spontaneously with resumption of evacuation activity. Relief of pain after the ingestion of food appears to be related to the change from resting to the motor activity of evacuation. Relief of pain after vagotomy and after the administration of cholinergic blocking agents appears to be related to their inhibitory effect on the gastrointestinal motor activity.

The authors feel that these data do not support the concept that ulcer pain is produced by direct chemical irritation by hydrochloric acid. The mucosal engorgement accompanying the ulcer may lower the threshold to hydrochloric acid, permitting the acid and perhaps other stimuli to initiate the reflex disturbance in the motor activity of the stomach and duodenum, which appears to be the direct cause of ulcer pain.

The higher doses will cause a slight increase in the frequency of mild side-reactions. Triethylene thiophosphoramide (Thio-Tepa), one of the newer nitrogen mustard compounds, showed promise among the nonradioactive agents.

Some Observations on the Treatment of Postirradiation Hematopoietic Depression in Man by the Infusion of Stored Autogenous Bone Marrow. N. B. Kurnick, B. H. Feder, A. Montano and others. Ann. Int. Med. 51:1204-1219 (Dec.) 1959 [Lancaster, Pa.].

The authors say that continuation of their studies on the transplantation of donor bone marrow did not cause them to alter their opinion that donation of bone marrow in man has no more than a transitory success, lasting up to a few weeks at best. It is not possible to assure that immune mechanisms of the recipient will not result in the rejection of the donated tissue. Suppression of immune responsiveness by roentgen irradiation does not seem possible in man at dosages below those which severely damage many tissues. Furthermore, even if transplantation should be successfully performed, homologous disease is likely to ensue, due to the production of antibodies by the donated leukocytes against the recipient's tissues.

To avoid these difficulties, the authors resorted to the repopulation of suppressed marrow with stored autologous marrow, i. e., the patient's own marrow. Approximately 60 ml. of marrow is aspirated from the posterior iliac crest, and the aspiration is repeated in the opposite ilium. Pending the collection of adequate information on the number of marrow cells required for repopulation of the marrow, the authors seek to collect 2.5 to 3×10^9 nucleated marrow elements. This goal is generally exceeded by the collection of 120 ml. of marrow, and rarely is it necessary to repeat the procedure. The procedure is well tolerated by ambulatory patients. After adding glycerol in tissue culture medium, the marrow is frozen, first at the rate of 1 C per minute to —29 C (—20.2 F) and then at the rate of 2 or 3 C per minute to —79 C (—112 F). The marrow is stored at —79 C in a dry ice chest.

The authors report on 14 patients with malignant disease who received extensive radiotherapy 6 months to 2 years ago and whose bone marrow was stored prior to irradiation. Four of these patients received 5 reinfusions of their own bone marrow; the remaining 10 were not reinfused because of the relatively mild blood count depression, and this group served as controls. To illustrate the results obtained, the authors describe observations on 2 patients into whom the stored bone marrow was reinfused, and 2 controls in whom this was not done. They found that regeneration and hyperplasia of severely radiation-depressed marrow occurred in 1½ to 4 weeks after the infusion of stored autologous bone marrow. It is their opinion that the preservation and subsequent reinfusion of autologous bone marrow are a safe and effective adjunct to the therapy of malignant disease with bone marrow suppressive agents, including radiation and chemical agents. The banking of marrow of persons whose occupations entail hazard of excessive radiation would also appear to be a reasonable precaution.

PHYSIOLOGY

The Role of the Gastric Antrum in the Regulation of Gastric Secretion. E. R. Woodward. Gastroenterology 38:7-14 (Jan.) 1960 [Baltimore].

Effects of antrum resection and transplantation on gastric secretion were studied in 2 groups of dogs. Isolated small stomach pouches of the Pavlov or Heidenhain variety were prepared in a series of 11 mongrel dogs. After recovery from surgery, continuous daily collections were made of the gastric juice secreted by the isolated pouches. After long periods of observation, the animals were subjected to reoperation, and resection of the gastric antrum was performed. After recovery from surgery, collections of pouch secretion were resumed. Resection of the antrum was followed by drastic reduction in the secretion of acid gastric juice by the isolated stomach pouch in every animal. The reduction varied from 64 to 95% and averaged 84%. These results seem to indicate that the major stimulus responsible for the secretion of acid gastric juice by the isolated stomach pouch was related to the presence of the antrum.

In another group of 8 dogs the antrum was transplanted in stages in order to sever completely its extrinsic nerve supply. The animal preparation used was a totally isolated stomach pouch with the vagi cut. After a long observation period during a second operation, the antrum was separated from the remainder of the stomach, with preservation of the posterior wall and the lesser curvature. The antral segment was then sutured as a diverticulum into a window created in the duodenal wall. The antral transplant was completely separated from its original blood and nerve supply at a third operation. Gastric secretion was meager during the first phase. When a stoma was created between the antrum and the duodenum, the daily gastric secretion increased from less than 5 mEq. of hydrochloric acid to nearly 100 mEq. When the antrum was completely denervated, high levels of gastric secretion were maintained, although at a slightly lower level. These findings demonstrate that after complete interruption of the extrinsic nerve supply to the antrum, as well as complete separation of its neuromuscular connections to the remainder of the stomach, exposure to the contents of the duodenum powerfully stimulates the body of the stomach to secrete acid gastric juice.

plates were made possible by the generosity of several manufacturers of pharmaceuticals, thus helping to keep the cost of the book within reasonable limits. Unfortunately, a few of these plates are out of focus or represent such extreme close-ups that it is difficult for the reader to orient himself properly despite the use of line drawings to indicate the region photographed. The volume is recommended for the physician who is unable to devote adequate time to the subject of skin diseases. It is hoped, however, that medical students will read more complete textbooks and become more learned in this field than would be possible from a study of this monograph.

Ervin Epstein, M.D.

Smoking and Health. By Alton Ochsner, M.D. Cloth. $3. Pp. 108, with illustrations. Julian Messner, Inc., 8 W. 40th St., New York 18; Copp Clark Publishing Company, Ltd., 495-517 Wellington St., W., Toronto 2B, Canada, 1959.

Since publication of an earlier volume on smoking and cancer, Dr. Ochsner has assembled additional data on the production of numerous diseases or abnormalities in health. The first chapter presents data assembled by Dr. H. F. Dorn of the National Institutes of Health in 1959. Dr. Dorn's figures were obtained from 200,000 veterans and indicated that among heavy smokers the death rate (from all causes) was almost twice that of nonsmokers. The death rate from lung cancer among men who smoked more than one pack of cigarettes a day was 16 times the rate for nonsmokers. The death rate from coronary disease was 63% higher among the smokers. The incidence of numerous other diseases is also increased by cigarette smoking. He criticized the tobacco industry for its feeble efforts in investigating this problem and denounced their clever advertisements, which avoid recognition of the dangers of cigarette smoking.

The author emphasized the relationship between the increase in cigarette smoking and the increase in lung cancer. In 1910 when lung cancer was uncommon the average per capita consumption of cigarettes was only 139, but in 1955 it was 3,000.

Some of the recent experimental chemical data on the presence of carcinogens in tobacco smoke were presented. Eight carcinogens have already been identified in tobacco smoke. Experiments of Wynder and associates revealed that if the temperature in the burning tobacco was decreased from the usual temperature of about 800 to 540 C, the carcinogenic effect in mice was reduced from 67 to 3%. The seriousness of cancer of the lung was emphasized by the fact that in a large series of cases only 60% were operable and 36% were resectable; 26% of the patients survived resection but only 8% were alive at the end of five years.

The author commended the courage of London's health officer who ordered the following announcement to be posted on large yellow signs all over the city: "It is my duty to warn all cigarette smokers that there is now conclusive evidence that they are running a greater risk of contracting cancer than nonsmokers. The risk mounts with the number of cigarettes smoked. Giving up smoking reduces the risk."

All this information is presented in such a convincing way that it is difficult to understand how one could read this book and continue smoking.

Warren H. Cole, M.D.

Antibiotic and Sulphonamide Treatment: A Short Guide for Practitioners. By A. R. Anscombe, M.S., F.R.C.S., D. B. Brown, M.B., M.M.S.A., M.R.C.O.G., and D. M. Davies, M.R.C.P. Edited by M. E. Florey, M.D. With foreword by The Rt. Hon. The Lord Evans, G.C.V.O., M.D., F.R.C.P. Cloth. $2.75. Pp. 150. Oxford University Press, Amen House, Warwick Sq., London, E. C. 4, England; 417 Fifth Ave., New York 16, 1959.

This compact little volume contains a wealth of information gathered from many sources and put together with skill. After a few brief pages on such topics as the sensitivity and resistance of microorganisms to antibiotics and the use of antibiotics in combination, the individual antibiotics and sulfonamides are considered under the following headings: characteristics, pharmaceutical preparations available, dosage, indications, and untoward reactions. The more common infections are considered according to the organ system involved.

In general, the drugs are those that are in common use in this country although, unfortunately, some of the antibiotics that have been recently introduced in this country, such as ristocetin, kanamycin, amphotericin, and dimethylchlortetracycline, have not been included. Occasionally the official names differ. The recommendations coincide with those that would be made in the leading clinics in the United States, except for a few discrepancies. For instance, sulfonamides are recommended by the authors in the treatment of pneumococcic pneumonia unless the patient is severely ill. Most clinicians in this country prefer to use penicillin or tetracycline as it has been shown that the fatality in this disease is twice as high when the sulfonamides are used. The poorly absorbable sulfonamides are recommended in bacillary (Shigella) dysentery, although I believe sulfadiazine has been shown to be superior. Furthermore, there is no evidence that antibiotics prevent the development of pneumonia in patients with tetanus.

These are minor discrepancies of the kind that are bound to occur among different authorities in any field, especially one which is changing as rapidly as is the field of infectious diseases. The book is to be recommended highly to general practitioners for whom it is intended as a handy and useful guide.

Harry F. Dowling, M.D.

BOOK REVIEWS

Christopher's Minor Surgery. Edited by Alton Ochsner, M.D., F.A.C.S., Professor of Clinical Surgery, Tulane University School of Medicine, New Orleans, and Michael E. DeBakey, M.D., F.A.C.S., Professor of Surgery and Chairman, Department of Surgery, Baylor University College of Medicine, Dallas. *Eighth edition. Cloth. $10.50. Pp. 539, with 347 illustrations.* W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, England, 1959.

In this edition of Christopher's well-established work, the latest thinking, mainly from Tulane and Baylor universities, has brought the text up to date. A large subject has been presented in a well-edited and orderly manner. The authors sharply delineate minor from major surgery, but they have presented a book which thoroughly covers surgical practice for practically every condition treated in the office or the outpatient clinic. The more recent knowledge of vascular diseases has been given more adequate coverage. New chapters on hand injuries, diseases of the breast, and physical treatment are well written and should be helpful in the treatment of patients.

The erudite and philosophical chapter on the surgical resident should be read by all interns and residents. In a few pages it covers the traditional "do's" and "don'ts" for the house staff. The author correctly names the chief need for residents who wish to acquire surgical skill. They must be attentive. I feel that surgical technique cannot be learned completely merely by assisting; perhaps if more visiting surgeons in teaching hospitals had the time or interest to assist the resident from across the table, better training would result.

Cardiac arrest may be seen by anyone performing operations, whether major or minor, so the technique should be understood by every surgeon. The discussion of this subject could be more detailed and more emphasis could have been placed on the points Beck is currently making in films and literature, namely, that the time limit is four minutes and that massage must be gentle to avoid injury to the myocardium.

The book is practical; it has the needed step-by-step directions; and it has an interesting style so that it is easy to read rapidly. Enough etiological and pathological material has been included, and superfluous or controversial material has been omitted. Some of the illustrations could be improved. The book is thorough and authoritative and can be recommended to every physician seeing surgical patients.

Irving Thrasher, M.D.

Manual of Skin Diseases. By Gordon C. Sauer, M.D., Assistant Clinical Professor of Medicine (Dermatology) and Chief of Section of Dermatology, University of Kansas School of Medicine, Kansas City. Cloth. $9.75. Pp. 269, with 179 illustrations. J. B. Lippincott Company, E. Washington Sq., Philadelphia 5; 4865 Western Ave., Montreal 6, Canada; Pitman Medical Publishing Company, Ltd., 39 Parker St., London, W. C. 2, England, 1959.

In this interesting book an attempt is made to reduce the subject of dermatology to its essentials. The author says that at least one medical student expressed the desire for a 50-page book on skin diseases. While the present trend in writing medical books is to produce compact volumes instead of the massive tomes of yesteryear, this too can be overdone. The practice of dermatology has become much more than arriving at a descriptive diagnosis and treating the patient with an empirical application. Over-simplification can only lower the status of this specialty while lulling the practitioner into a sense of false security that camouflages his lack of understanding of the common, troublesome dermatoses.

The author presents many original innovations that make his manuscript interesting and easy to read. The publisher must be congratulated for the beautiful paper, printing, and binding that have gone into this volume. Among the new features might be mentioned the "dictionary-index" that lists not only the pages on which the sought-after discussion can be located but, in the case of rare diseases and therapeutic agents, a short definition or description of it.

An interesting feature is the "play-by-play" description of how one interviews a patient with an eruption on her hands. Many practitioners find it difficult to establish what questions to ask a dermatological patient. The author attempts to consider cutaneous derangements from many aspects including topography (regional distribution); geography (endemic areas); age incidence (pediatric geriatric); race (Negro); and occupation (military) Unfortunately, incompleteness robs these section of much of their potential value. In the chapter o therapeutics blank pages are provided so that th reader may add his own favorite prescriptions. I some places, notably the discussions of therapy an syphilis, important principles are grouped an labeled as "pearls."

There are statements that cannot be accepted a established facts. For example, "in normal times scabies is rarely seen except in school children c in poor people under crowded conditions." Th illustrations are outstanding. The excellent col included any that could be associated with the production of neuritis (e. g., sulfonamides) and (2) the man's preferred hand.

This patient's case should be studied by a neurologist and a psychiatrist, preferably on a neurological ward. While a thorough neurological examination may be difficult to accomplish, such objective sensory evaluation as can be achieved is necessary, including cortical sensory studies. Tenderness of the muscles to deep pressure, one of the cardinal signs of polyneuritis, should be looked for. Since so many of the patient's sensory avenues are "blocked," electroencephalography and other neurological and psychiatric laboratory tests may shed light on his case.

Although the patient's auditory deficit is likely to make communication with him difficult, thorough neurological and psychiatric evaluation should nevertheless be attempted, with the aid of up-to-date laboratory techniques for study of the sensory paths. Teuber of New York University and Bender of Mt. Sinai Hospital have done considerable research on sensory functions (see Bender, L.: Disorders in Perception, with Particular Reference to the Phenomena of Extinction and Displacement, Springfield, Ill., Charles C Thomas, Publisher, 1952, p. 109).

HYPERHIDROSIS

To THE EDITOR:—*A 62-year-old patient suffers from excessive nocturnal sweating, which started about three weeks after a suprapubic prostatectomy for hypertrophy of the middle lobe. The sweating is now less severe but occurs frequently during the day. The patient's general physical condition is good, and there is no evidence of a cause for the hyperhidrosis. Could an endocrine imbalance due to the prostatectomy be the basis of the hyperhidrosis?* *M.D., New York.*

ANSWER.—Since no essential endocrine function has been attributed to the prostate, its removal is not likely to have an endocrine effect resulting in hyperhidrosis. Other causes for the patient's complaint, such as some vasomotor instability or any drugs he may be taking, should be suspected. Excessive formation of perspiration is probably not a specific reaction to or sequela of the prostatectomy per se.

ANSWER.—The occurrence of hyperhidrosis is not unusual in persons convalescing from severe acute diseases and in debilitated persons generally. One explanation for the condition is an increased responsiveness of the sweat glands to customary nervous and non-nervous stimuli. An endocrine disturbance would seem an unlikely cause. There is no specific treatment for hyperhidrosis (subcutaneous injection of acetylcholine to produce "paradoxical anhidrosis" having long been discarded). Studies should be carried out to determine if unusual responsiveness of the sweat glands does exist, and, if so, the patient should be advised how to avoid exposure to the usual sudorific stimuli.

SPONTANEOUS REGRESSION OF TUMORS

To THE EDITOR:—*Is there any evidence, clinical or statistical, that infection of a malignant tumor can produce regressive change or spontaneous elimination of the cancer?* *M.D., Illinois.*

ANSWER.—There is considerable clinical and statistical evidence that acute infection may produce regressive changes in malignant tumors. Physicians have observed these changes for over 200 years. The phenomenon has also been observed to take place in patients after they have had severe thermal burns, high fevers of unknown origin, acute inflammatory reactions, or fractures. Several recent articles by Nauts, Swift, and Coley review this subject, namely, the treatment of malignant tumors by bacterial toxins as developed by Coley (*Cancer Res.* 6:205 [April] 1946); a review by Nauts, Fowler, and Bogatko of the influence of bacterial infection and bacterial products (Coley's toxins) on malignant tumors in man (*Acta med. scandinav.*, supp. 276, p. 103, 1953); and a discussion by Pelner, Fowler, and Nauts of the effects of concurrent infection and these toxins on the course of leukemia (*ibid.*, supp. 338, p. 47, 1958).

There is, of course, some doubt whether the changes noted are due to spontaneous regression or to stimulation of host resistance. Much work is being done to elucidate this question. The consensus is that, while some cases are probably examples of spontaneous regression, most are due to some stimulation of host resistance by a factor or factors unknown.

CONGENITAL FISTULA OF LACRIMAL SAC

To THE EDITOR:—*What is the incidence and treatment of congenital openings that drain a tear-like fluid and are located along the nose just inferior to the medial canthus of the eye? In a 6-year-old child with this anomaly the openings are bilateral but do not drain continuously and are not infected.*

James D. Klein, M.D., Clarkston, Wash.

ANSWER.—Openings in this area are usually congenital fistulas of the lacrimal sac and occur relatively frequently. The opening is small and often occurs bilaterally. This developmental aberration usually gives rise to few symptoms and is often overlooked in early life. The fluid that drains is usually clear; occasionally, however, a mucopurulent discharge is present. Lacrimal fistulas should be closed either by cautery or by operation. The lacrimal sac and the nasolacrimal duct should first be probed to make sure that the duct is patent.

QUESTIONS AND ANSWERS

SEVERE AND FATAL REACTIONS TO TRANQUILIZERS

To the Editor:—*An oophorectomy (left side) and appendectomy were performed on a 19-year-old girl as an elective surgical procedure. She tolerated the operation well, responded satisfactorily to the anesthesia, and was sent from the recovery room in good condition, in a lucid state and able to talk. About five hours after receiving an intramuscular injection of 5 mg. of perphenazine she had a convulsive seizure, became unconscious, and developed anisocoria and hemiparalysis. Neither her blood pressure nor her pulse rate indicated a state of shock, and her urinary output was adequate. Results of a spinal tap showed no significant changes. About three hours after onset of these complications the patient developed marked pulmonary edema, went into shock, and died. The only significant autopsy findings were cerebral edema and marked pulmonary edema. It appears that the pulmonary edema was secondary to the cerebral edema, but the etiology of the latter was undetermined. It has been reported that tranquilizers have produced central nervous system symptoms. Is it possible that so small an amount of perphenazine could cause such a reaction?*

C. M. Karpas, M.D., Miami, Fla.

Answer.—According to Wang (*J. Pharmacol. & Exper. Therap.* 123:306 [Aug.] 1958), perphenazine is 17 to 50 times more potent an antiemetic than chlorpromazine hydrochloride and more widespread in its antiemetic action, since it will prevent the emesis induced by emetics other than apomorphine hydrochloride. The 5-mg. intramuscular dose of perphenazine which produced a fatal convulsion in this 19-year-old patient postoperatively might logically be compared to an intramuscular dose of 17 to 50 times 5 mg., or 85 to 250 mg., of chlorpromazine given intramuscularly; by this comparison, the 5-mg. dose is not small. The inquirer should consult Graff and associates (J. A. M. A. 169:834 [Feb. 21] 1959) for a report of a similar convulsive state that was induced by 8 mg. of perphenazine given orally twice a day. Clonic convulsions occurred after the third dose. Administration of the perphenazine was discontinued, and the patient was successfully treated with phenobarbital. Barrett (*J. A. M. A.* 166:1986 [April 19] 1958) reported convulsive seizures as a side-effect of chlorpromazine therapy, and numerous laboratory workers have shown that the three clinically useful alkaloids of rauwolfia and chlorpromazine will effectively lower the threshold for electroshock in rats and mice. Convulsions as a side-effect of therapy with the two substituted phenothiazines thus are to be expected, and these seizures should be treated vigorously with parenterally given phenobarbital, as in the treatment of status epilepticus. In the instance reported above, both the anisocoria and hemiparalysis were probably due to a series of convulsive seizures (or subclinical seizure activity) which produced cerebral edema. Freyhan (*Am. J. Psychiat.* 115:577 [Jan.] 1959) found perphenazine to be one of the most active of the phenothiazines in the production of paralysis agitans in schizophrenic patients.

NEUROLOGICAL SEQUELAE OF MENINGITIS

To the Editor:—*Since his recovery from meningococcic meningitis, a 72-year-old man has had a definite hearing defect and complete numbness in the finger tips. Since he is also blind, he depends on his senses of hearing and touch. His occupation requires handling of merchandise and coins, which he distinguishes by touch, so that the return in finger tip sensation is extremely important to him. He can button his clothing with his left hand but not with his right. A psychiatrist concluded that the loss of the finger tip sensation is psychological in origin; perhaps induced by fear, since the patient is forced to depend on finger tip sensation and hearing to earn his livelihood. What help can this patient be given?* *John T. Myers, M.D., New York.*

Answer.—Bilateral deafness may develop suddenly in patients with meningococcic meningitis, usually in the second week; it remains permanently in about 2% of patients. The incidence of focal neurological complications is about 1%. Nerve roots or the spinal cord may become involved by direct extension of the inflammatory process from the leptomeninges.

It is impossible to resolve the problem of this 72-year-old man with the information at hand. Among many data that are lacking for evaluation of the return of sensation in the left hand rather than the right are (1) the names of the drugs used in treating the meningitis, namely, whether they

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The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

WASHINGTON NEWS

Forand Bill Developments . .
Hit Drug Hearings . .
Physicians Under Social Security . .
Senate Hearings on Aged . .

FORAND BILL REMAINS BIG ISSUE

Although the House Ways and Means Committee put off consideration of changes in social security during Easter week, health care for the aged continued to stir controversy in Congress.

The two major developments were (1) introduction of a measure by eight Republican senators to provide federal-state payments to assist the needy aged to purchase private health insurance and (2) the renewed promise by Arthur S. Flemming, Secretary of Health, Education, and Welfare, that the administration would formally propose its own program in the field this congressional session.

Flemming, called to speak again before the Senate subcommittee on aging headed by Sen. Pat McNamara (D., Mich.), also repeated the administration's opposition to the compulsory Forand approach through the social security system. Despite reports to the contrary, he testified, there was complete agreement within the administration on this point.

Flemming indicated strongly that any administration plan would be similar to that offered by the eight Republican senators, although probably not as broad. The legislation, sponsored by senators Jacob Javits (R., N. Y.), High Scott (R., Pa.), and six other GOP lawmakers, would cost the federal government about 500 million dollars a year. Under the voluntary program, the states would put up about 640 million and subscribers about 400 million dollars.

Flemming called the measure a "step in the right direction" but said it had not yet been thoroughly studied by the administration. Senator Javits told reporters the administration "may feel the coverage is too broad and costs too much."

"The administration could, if it chose, take this bill as a basis and possibly make some recommendations for revision," he said. "Our bill conceivably can turn out to be an administration bill, but I understand they bridle at the amounts."

Introduction of the GOP senators' bill further complicated the legislative situation on health care of the aged. In addition to this measure and any administration program, there were still powerful drives for the Forand plan of widening the social security system to include health care for the first time.

Another program being discussed by some lawmakers would expand the present federal-state public assistance program to provide additional health care for persons judged medically indigent.

An important action will be the final decision of the House Ways and Means Committee on what type of medical bill, if any, it will approve. The Committee has already rejected the Forand measure. Once any type of bill involving changes in social security reaches the Senate—and this appears to be a certainty—there would be the danger of an attempt to include the Forand bill on the Senate floor.

Organized labor made it plain that its main goal was passage of the Forand legislation. United Auto Workers President Walter Reuther organized a "march" of some several hundred union members on the Capitol to urge enactment of the controversial bill opposed by the American Medical Association and many other groups. Labor leaders criticized the Republican senators' bill as "inept."

DRUG HEARINGS RESUME

Sen. Estes Kefauver (D., Tenn.) called individual physicians to give their views on drug industry practices, as the Republican members of his Senate antitrust subcommittee labeled the investigation "headline hunting" and "misleading."

Senate minority leader Everett M. Dirksen (R., Ill.), in a sharp exchange, told Kefauver he was not going to sit idly by and watch "a whole industry indicted by a Senate subcommittee." And Sen. Roman L. Hruska (R., Neb.) contended "there has been a deliberate attempt to inflict devastating and irreparable damage upon an indispensable business by trying hard to shatter public confidence in it upon the basis of a biased, distorted, and incomplete record."

Kefauver replied that "there is not going to be a whitewash of anything" and that he would continue to press the inquiry.

Both Dirksen and Hruska charged that the physicians called to appear before the subcommittee had almost without exception been known to be antagonistic to the drug industry. "These witnesses have not been representative, either officially or in fact, of their profession," said Hruska. "In the main they have represented nonconforming, antagonistic views, clearly not held by the great preponderance of their professional brethren."

Kefauver declared that the subcommittee had received hundreds of letters from individual physicians and that most of them favored the purpose of the investigation. The American Medical Asso-

(Continued on next page)

Spontaneous healing of the fistulas occurs sometimes after repeated probing. The opening may be cauterized by electrocautery or by chemical means, such as application of silver nitrate or trichloracetic acid. Surgical closure consists of excision of the fistulous opening and closure by appositional sutures.

NITROGEN NARCOSIS IN UNDERWATER DIVERS

To the Editor:—*It has been shown that dextro amphetamine sulfate has an antagonistic effect on the analgesic action of nitrous oxide. This action suggests that d-amphetamine might counteract the depressing effect of nitrous oxide on the central nervous system. Since nitrous oxide is chemically related to nitrogen, it might also be possible to use this pharmacological characteristic of d-amphetamine to treat a person with nitrogen narcosis due to underwater diving. What effect does d-amphetamine have on nitrous-oxide narcosis as compared to nitrous-oxide analgesia? Has d-amphetamine been tested for its effect on a patient with nitrogen narcosis?*

Alfred B. Mason, M.D., Concord, Calif.

Answer.—The drugs of the amphetamine series have been thoroughly investigated in an effort to find agents that will reduce or abolish the narcotic effects of high partial pressures of nitrogen. To date there is no subjective or objective evidence that the symptoms of a patient with nitrogen narcosis are to any extent alleviated by administration of these drugs. The clinical events of nitrous-oxide anesthesia have been compared to those of nitrogen narcosis, but apparently they are not physiologically identical. Administration of amphetamine drugs might tend to enhance the already dangerous euphoria of the diver.

ADENOFIBROMA OF THE BREAST

To the Editor:—*In December, 1958, two adenofibromas, one the size of a small orange and the other the size of a large olive, were removed from the right breast of a 15-year-old girl. A follow-up examination indicated the presence of a new growth, in the same breast, about the size of a small olive and located in the upper inner quadrant. Apart from a nasal allergy, the girl's health is excellent. What course should be followed?*

M.D., Texas.

Answer.—Adenofibromas usually develop in the breasts of girls and younger women, the average age of these patients being 21 years. These lesions appear and increase in size in young girls, possibly because of hormonal activity; this does not, however, indicate a hormonal dysfunction in these patients. Neither hormone studies nor hormonal treatment are necessary. Adenofibromas can easily be excised or enucleated, without altering the normal appearance of the breast. They should be removed to establish the histological identity of the tumor. Even when previously removed tumors were proved to be adenofibromas, any new or recurrent tumor also should be excised for histological study.

GRANULATION TISSUE

To the Editor:—*Please outline the best treatment for granulation tissue formed in the vaginal vault after hysterectomy.* *M.D., Tennessee.*

Answer.—Formation of granulation tissue in the vaginal vault after hysterectomy occurs in 20 to 30% of cases. The most satisfactory treatment is to excise the granulation tissue and then treat the area very lightly with electrocautery. Small areas of granulation tissue can be treated with electrocautery alone. Usually the patient feels little or no discomfort from this procedure.

CHEWING GUM IN EYELASHES

To the Editor:—*A four-year-old boy had his eyelashes plastered with chewing gum and his mother was unable to remove it. Can you suggest any treatment?*

Tom Sparks, M.D., Ardmore, Okla.

Answer.—The only remedy appears to be to cut the eyelashes. Carbon tetrachloride might act as a solvent but is too toxic for application about the eyes.

HYDROCELE

To the Editor:—*In reference to the cause and treatment of hydrocele in a 7-year-old child given in* The Journal, *Jan. 23, page 408, the reply should have made reference to the fact that the most common cause (excluding trauma) of hydrocele in this age group is the presence of a thin-walled, narrow-caliber inguinal hernial sac in communication with the tunica vaginalis. The treatment for this condition is herniorrhaphy.*

Frank J. Rack, M.D.
Parma Medical Center
5500 Ridge Rd.
Cleveland, Ohio.

The above comment was referred to the consultant who answered the original question, and his reply follows:—Ed.

To the Editor:—*The question raised in the physician's criticism concerns a condition entirely different from hydrocele. The lesion he speaks of is a patent funiculus, in which the swelling comes and goes. It is not a true hydrocele. Other urologists agree that the lesion, as described in the comment, is not a true hydrocele.*

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NILEVAR Builds Protein, Speeds Convalescence to Complete Recovery[3-6] ". . . we were impressed[3] with the efficacy of Nilevar as an anabolic agent. All of the patients reported feeling much more vigorous and experiencing an increase in appetite. . . ."

The actions of Nilevar[4] in reversing a negative nitrogen balance—and therefore a negative protein balance—improving the appetite and increasing the sense of well-being can be expected to shorten the illness and the convalescence of these patients.

An initial daily dosage of 30 mg. of Nilevar (brand of norethandrolone) is suggested. After one to two weeks, this dosage may be reduced to 10 or 20 mg. daily in accordance with the response of the patient. Continuous courses of therapy should not exceed three months, but may be repeated after rest periods of one month. Nilevar is supplied as tablets of 10 mg., drops of 0.25 mg. per drop and ampuls of 25 mg. in 1 cc. of sesame oil with benzyl alcohol.

1. Eisen, H. N., and Tabachnick, M.: Protein Metabolism, M. Clin. North America 39:863 (May) 1955. 2. Jamison, R. M.: General Nutritive Deficiency, Virginia M. Month. 83:67 (Feb.) 1956. 3. Goldfarb, A. F.; Napp, E. E.; Stone, M. L.; Zuckerman, M. B., and Simon, J.: The Anabolic Effects of Norethandrolone, a 19-Nortestosterone Derivative, Obst. & Gynec. 11:454 (April) 1958. 4. Batson, R.: Investigator's Report, Feb. 11, 1956. 5. Weston, R. E.; Isaacs, M. C.; Rosenblum, R.; Gibbons, D. M., and Grossman, J.: Metabolic Effects of an Anabolic Steroid, 17-Alpha-Ethyl-17-Hydroxy-Norandrostenone, in Human Subjects, J. Clin. Invest. 35:744 (June) 1956. 6. Brown, C. H.: The Treatment of Acute and Chronic Ulcerative Colitis, Am. Pract. & Digest Treat. 9:405 (March) 1958.

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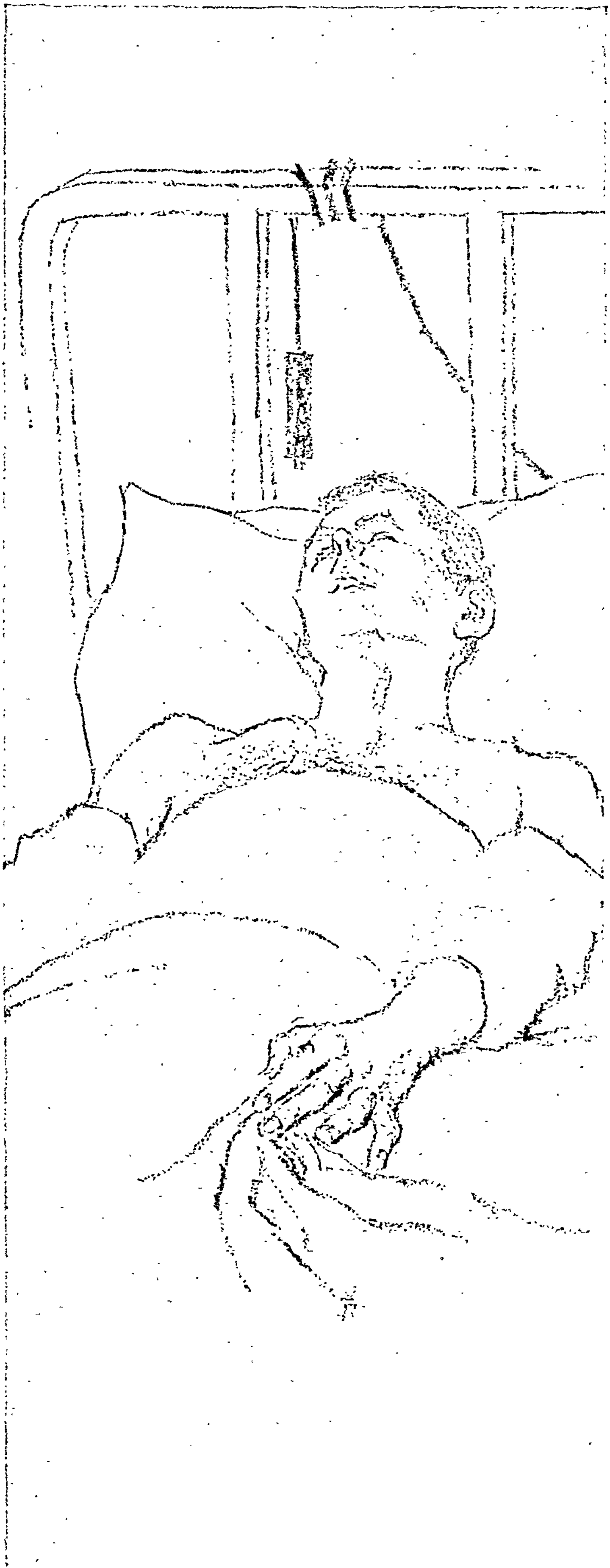

ciation, he said, would present its views later when some legislative proposals are drafted by the subcommittee.

Dr. William Bean of the University of Iowa School of Medicine told the subcommittee that he was "deeply concerned" about firms which "do not use scrupulous caution" in releasing new drugs. He also charged that some medical journals have refused to publish articles criticizing particular drugs, lest advertising suffer.

Dr. Frederick H. Meyers of the University of California said that most of the progress in developing new drugs has come from Europe. "It appears that our industry has usually followed and often after a clear lag," he said.

Dr. A. Dale Console, former medical director of Squibb Laboratories, said that physicians and the public are subjected to a "constant barrage" of new drugs even though "some are worthless and others have a greater potential for harm than for good." He said the drug industry is "unique in that it can make exploitation appear a noble purpose." He asserted the industry has a simple maxim in selling its products: "If you can't convince them, confuse them."

Senator Hruska said that his contentions amounted to a "severe indictment" and that he unfairly painted the average doctor as "a simpleton and quite a gullible fellow."

Earlier, the lawmaker had said, "I find myself wondering why it is that the voices of thousands upon thousands of doctors who rightly credit the drug industry with many solid and remarkable achievements have not already been called in timely fashion."

The drug hearings had been discontinued during the Senate debate on civil rights, but they resumed after House passage of a civil rights measure. nator Kefauver did not disclose what legislative posals the subcommittee was considering.

OPPOSE PHYSICIANS UNDER SOCIAL SECURITY

The House Ways and Means Committee was urged to reverse its tentative vote to provide for the compulsory inclusion of physicians under the social security system. In a letter to the committee, Dr. F. J. L. Blasingame, Executive Vice-president of the American Medical Association, said that the A. M. A.'s House of Delegates since 1949 has consistently gone on record in opposition to forcing physicians under social security.

Social security, said Dr. Blasingame, "does not fit the economic pattern of the practicing physician. Self-employed doctors rarely retire at age 65. Therefore, the compulsory tax which would be imposed on them, were they covered under the social security system, would be unjust and unreasonable," he declared.

"Physicians who are able to work prefer to keep right on practicing medicine," continued Dr. Blasingame. "A survey of this point shows that over 85% of the doctors between the ages of 65 and 72 are in active practice. Over 50% of the physicians who retire do so after the age of 74. Thus, if forced under this program, the typical physician would be required to pay Social Security taxes until age 72 before he would receive benefits.

"Finally, and perhaps most important, physicians have seen social insurance programs in other nations used as a vehicle for the establishment of socialized medicine. They have fought against the Murray-Wagner-Dingell bills of 1949 and the Forand bills of today. They know that the OASDI (Old Age and Survivors' Disability Insurance) system constitutes the principal avenue by which socialized medicine advocates hope to achieve their goal. Naturally, they are highly sensitive to their inclusion in a system which may eventually be used to abridge their freedom as a profession."

The Ways and Means Committee tentatively voted the inclusion of physicians under social security as part of its work on amending the over-all social security program. The administration had recommended forcing physicians into the program at the start of the committee's sessions.

In his letter to the Committee, Dr. Blasingame noted that many state medical associations have polled their members on the question of compulsory coverage, and "It can be concluded from the results that a majority of the professions is still opposed to compulsory coverage."

SENATE COMMITTEE PLANS FURTHER HEARINGS ON AGED

The Senate subcommittee on aging, which recently issued a highly controversial report recommending a sweeping federal program for the aged including a broad government health plan, was voted $85,000 by the Senate to continue its investigation of aged problems.

Sen. Pat McNamara (D., Mich.), chairman of the subcommittee, said that for the rest of the year the group will, among other things, call in federal officials to discuss various aspects of the investigation and hold hearings both here and in cities throughout the country. A final report will be prepared by Jan. 31, 1961, he said.

Fields of inquiry listed were:

1. Reducing the number of older persons entering mental institutions and staying there.
2. Improving the quality of nursing home care.
3. Increasing employment opportunities for older workers.
4. ". . . Ways and means of organizing medical programs in the home so as to avoid the heavy cost of hospitalization."
5. Enabling the elderly to be useful for community work.
6. A study of community services which can assist older persons, when needed, to remain in their own homes and to live independently and self-reliantly as long as possible.
7. Retirement preparation and education.
8. Proposals for an office of the aging in the federal government.

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IDIOPATHIC THROMBOCYTOPENIC PURPURA

AN EVALUATION OF THE PATTERNS OF RESPONSE TO VARIOUS THERAPIES

William B. Scharfman, M.D., Henry F. Hosley, M.D., Thomas Hawkins, M.D.
and
Simon Propp, M.D., Albany, N. Y.

Laboratory findings, responses to medication, and results of surgery were studied in 24 children and 26 adults with idiopathic thrombocytopenic purpura (ITP). Splenectomy was never performed as an emergency measure in this series; the medical treatment with steroids and platelet transfusions in every instance changed the emergency situation into one permitting more deliberate measures. Splenectomy was performed on 23 patients, 16 of whom were receiving steroids. In the other 27 patients no surgery was done; 24 improved with medical treatment and 2 had spontaneous remissions. These patients, frequently children, had acute cases predominantly. The follow-up data available from 47 patients showed that 42 were in complete remission when last seen. There was one death. Seven case histories illustrate the need for individualizing the treatment.

THIS report concerns 50 consecutive patients with idiopathic thrombocytopenic purpura (ITP) treated at the Albany Hospital over a period of about five years. Much has been written about this disease in the recent literature with respect to etiology and pathogenesis.[1] Our particular interest in this group of patients, however, is in attempting to analyze the results which are obtained with the therapeutic measures currently in use. Our conclusion about these patients is that the intelligent use of platelet (or fresh blood) transfusions, steroids, and splenectomy, either alone or in combination, produces satisfactory results. It is difficult to predict the eventual outcome in an individual patient with a particular therapy but this study supports the medical adage that individualized treatment is the most effective course to follow.

It is not surprising that results of therapy are unpredictable in this hematological disorder, since at the moment its causation is still unknown. Despite the theories regarding pathogenesis, such as splenic hypersequestration, suppression of platelet production by the spleen via a humoral factor, and, more recently, autoimmune platelet antibody effect, this disease may be one of variable etiology and probably for this reason may respond differently to various therapies.

Criteria for Diagnosis

The criteria for the diagnosis of ITP are well recognized. A history is carefully taken, with special attention to drug sensitivity, particularly quinidine, and any possible exposure to myelotoxic drugs or chemicals. Recent acute infections and diseases which may produce thrombocytopenia, such as lupus erythematosus and cirrhosis, are investigated. Rare disorders like thrombotic thrombocytopenic purpura (we have seen three cases) are excluded from this study as are all the secondary thrombo-

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From the Department of Medicine and the Subdepartment of Hematology, Albany Medical College.

MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. F. J. L. Blasingame, 535 North Dearborn St., Chicago 10, Executive Vice-President.
1960 Annual Meeting, Miami Beach, Fla., June 13-17.
1960 Clinical Meeting, Washington, D. C., Nov. 28-Dec. 1.
1961 Annual Meeting, New York City, June 26-30.
1961 Clinical Meeting, Denver, Nov. 27-30.
1962 Annual Meeting, Chicago, June 11-15.
1962 Clinical Meeting, Los Angeles, Nov. 26-29.

AMERICAN

1960

April

Alabama, Medical Association of the State of, Admiral Semmes Hotel, Mobile, Apr. 21-23. Mr. W. A. Dozier Jr., 19 S. Jackson St., Montgomery 4, Executive Secretary.

American Academy of Neurology, Eden Roc Hotel, Miami, Fla., Apr. 25-30. Mrs. J. C. McKinley, 4307 E. 50th St., Minneapolis 17, Executive Secretary.

American Association of Pathologists and Bacteriologists, Hotel Peabody, Memphis, Tenn., Apr. 28-30. Dr. Russell L. Holman, Dept. of Pathology, L. S. U. School of Medicine, New Orleans, La., Secretary.

American College Health Association, Toronto, Canada, Apr. 27-30. Dr. Norman S. Moore, Cornell University, Gannett Clinic, Ithaca, N. Y., Secretary Treasurer.

American College of Sports Medicine, Saxony Hotel, Miami Beach, Fla., Apr. 22-24. Grover W. Mueller, M.S., Parkway at 21st St., Philadelphia 3, Secretary.

American Proctologic Society, Shamrock Hilton Hotel, Houston, Texas, Apr. 25-27. Dr. Norman D. Nigro, 10 Peterboro, Detroit 1, Secretary.

Andrew, John A., Clinical Society, Tuskegee Institute, Alabama, Apr. 24-29. Dr. Eugene H. Dibble, Memorial Hospital, Tuskegee Institute, Ala., Secretary.

Connecticut State Medical Society, Hamden High School, Hamden, Apr. 26-28. Dr. William R. Richards, 160 St. Ronan St., New Haven, Conn., Secretary.

Industrial Medical Association, Rochester, N. Y., Apr. 26-29. Mr. Clark D. Bridges, 28 E. Jackson Blvd., Chicago 4, Managing Director.

Iowa State Medical Society, Savery Hotel, Des Moines, Apr. 24-27. Mr. Donald L. Taylor, 529 36th St., Des Moines 12, Iowa, Executive Director.

Nebraska State Medical Association, Hotel Cornhusker, Lincoln, April 25-28. Mr. M. C. Smith, 1315 Sharp Building, Lincoln 8, Neb., ecutive Secretary.

Dakota State Medical Association, Dacotah Hotel, Grand s, Apr. 30-May 3. Mr. Lyle A. Limond, Box 1198, Bismarck, N. D., utive Secretary.

heastern Dermatological Association, Nashville, Tenn., Apr.)-May 1. Dr. Robert N. Buchanan Jr., 706 Church St., Nashville, Tenn., Organizing Physician.

May

Academy of Psychoanalysis, Hotel Claridge, Atlantic City, N. J., May 7-8. Dr. Joseph H. Merin, 125 E. 65th St., New York 21, Secretary.

Aerospace Medical Association, Americana Hotel, Bal Harbour, Fla., May 9-11. Dr. William J. Kennard, Aerospace Medical Association, Washington Natl. Airport, Washington 1, D. C., Secretary-Treasurer.

American Association for Cleft Palate Rehabilitation, Brown Palace Hotel, Denver, May 12-14. D. C. Spriestersbach, Ph.D., University Hospitals, Iowa City, Iowa, Secretary-Treasurer.

American Association of Genito-Urinary Surgeons, Dearborn Inn, Dearborn, Mich., May 11-13. Dr. William J. Engel, 2020 E. 93rd St., Cleveland 6, Secretary.

American Association on Mental Deficiency, Lord Baltimore Hotel, Baltimore, May 16-21. Mr. Neil A. Dayton, P. O. Box 51, Mansfield Depot, Conn., Executive Secretary-Treasurer.

American Association of Plastic Surgeons, Milwaukee Inn, Milwaukee, May 17-20. Dr. Thomas D. Cronin, 6615 Travis St., Houston 25, Texas, Secretary.

American Association for Thoracic Surgery, Deauville Hotel, Miami Beach, Fla., May 11-13. Dr. Hiram T. Langston, 7730 Carondelet Ave., St. Louis 5, Secretary.

American College of Cardiology, Indianapolis, May. Dr. Philip Reichert, 2709 Empire State Bldg., New York 1, Executive Director.

American Federation for Clinical Research, Chalfonte-Haddon Hall, Atlantic City, N. J., May 1. Mr. James E. Bryan, 250 W. 57th St., New York 19, Executive Secretary.

American Gynecological Society, Williamsburg Inn, Williamsburg, Va., May 30-June 1. Dr. Andrew A. Marchetti, Georgetown Univ. Hosp., Washington 7, D. C., Secretary.

American Ophthalmological Society, The Broadmoor, Colorado Springs, Colo., May 16-18. Dr. Maynard C. Wheeler, 30 W. 59th St., New York 19, Secretary.

American Orthopaedic Association, The Homestead, Hot Springs, Va., May 30-June 2. Dr. Lee Ramsay Straub, 535 E. 70 St., New York 21, Secretary.

American Pediatric Society, New Ocean House, Swampscott, Mass., May 5-6. Dr. Aims C. McGuinness, 2800 Quebec St., N. W., Washington 8, D. C., Secretary-Treasurer.

American Psychiatric Association, Inc., Hotel Traymore, Atlantic City, N. J., May 9-13. Dr. C. H. Hardin Branch, 156 Westminster Ave., Salt Lake City 15, Utah, Secretary.

American Psychoanalytic Association, Chalfonte-Haddon Hall, Atlantic City, N. J., May 6-9. Mrs. Helen Fischer, One E. 57th St., New York 22, Acting Executive Secretary.

American Society for Clinical Investigation, Haddon Hall, Atlantic City, N. J., May 1-2. Dr. Saul J. Farber, N. Y. U. College of Medicine, 550 First Ave., New York 16, Secretary.

American Trudeau Society, Statler and Biltmore Hotels, Los Angeles, May 16-18. Mr. Frank W. Webster, 1790 Broadway, New York 19, Executive Secretary.

American Urological Association, Inc., The Palmer House, Chicago, May 16-19. Mr. William P. Didusch, 1120 N. Charles St., Baltimore 1, Executive Secretary.

Arizona Medical Association, Inc., Safari Hotel, Scottsdale, Ariz., May 4-7. Mr. Robert Carpenter, 1021 Central Towers Bldg., Phoenix, Ariz., Executive Secretary.

Association of American Physicians, Haddon Hall, Atlantic City, N. J., May 3-4. Dr. Paul B. Beeson, Yale Univ. School of Medicine, New Haven 11, Conn., Secretary.

Association of Surgeons of the Southern Railway System, Charleston, S. C., May 9-10. Dr. Rudolph M. Landry, 707 Walnut St., Chattanooga 2, Tenn., Program Chairman.

Georgia, Medical Association of, Columbus, May 1-4. Mr. Milton D. Krueger, 938 Peachtree St., N. E., Atlanta 9, Ga., Executive Secretary.

Hawaii Medical Association, Honolulu, May 12-15. Mr. Lee McCaslin, 510 S. Beretania St., Room 200, Honolulu 13, Hawaii.

Illinois State Medical Society, Hotel Sherman, Chicago, May 24-27. Dr. George F. Lull, 185 N. Wabash, Chicago, Secretary.

Kansas Medical Society, Baker Hotel, Hutchinson, May 2-5. Mr. Oliver E. Ebel, 315 W. Fourth, Topeka, Kan., Executive Secretary.

Louisiana State Medical Society, Capitol House, Baton Rouge, May 2-4. Dr. C. Grenes Cole, 1430 Tulane Ave., New Orleans 12, Secretary-Treasurer.

Massachusetts Medical Society, Statler-Hilton Hotel, Boston, May 17-19. Mr. Everett R. Spencer Jr., 22 The Fenway, Boston 15, Director of Public Relations and Administration.

Medical Library Association, Inc., Muehlebach Hotel, Kansas City, Mo., May 16-20. Miss Nettie A. Mehne, Upjohn Company Library, 301 Henrietta St., Kalamazoo, Mich., Secretary.

Minnesota State Medical Association, Kahler Hotel, Rochester, May 23-25. Mr. Harold W. Brunn, 496 Lowry Medical Arts Bldg., St. Paul 2, Executive Secretary.

Mississippi State Medical Association, Hotel Heidelberg, Jackson, May 10-12. Mr. Rowland B. Kennedy, P. O. Box 4606, Fondren Station, Jackson, Miss., Executive Secretary.

National Tuberculosis Association, Statler & Biltmore Hotels, Los Angeles, May 15-20. Mr. James G. Stone, 1790 Broadway, New York 19, Executive Secretary.

Nevada Academy of General Practice, Reno, May 12-14. Dr. Roy M. Peters, 475 S. Arlington Ave., Reno, Nev., Program Chairman.

New Jersey, Medical Society of, Chalfonte-Haddon Hall, Atlantic City, May 14-18. Mr. Richard I. Nevin, P. O. Box 904, Trenton 5, N. J., Executive Officer.

New Mexico Medical Society, Western Skies Hotel, Albuquerque, May 10-13. Mr. Ralph R. Marshall, 220 First National Bank, Albuquerque, N. M., Executive Secretary.

New York, Medical Society of the State of, Statler-Hilton Hotel, New York City, May 7-13. Dr. Herbert T. Wagner, 750 3rd Ave., New York 17, Executive Director.

North Carolina Medical Society, Hotel Sir Walter, Raleigh, May 7-11. Mr. James T. Barnes, Capital Club Bldg., Raleigh, N. C., Executive Secretary.

Ogden Surgical Society, Ogden, Utah, May 18-20. Dr. O. E. Gra. 412 First Security Bank Bldg., Ogden, Utah, Secretary.

Ohio State Medical Association, Sheraton Cleveland, Cleveland, May 17-19. Mr. Charles S. Nelson, 79 E. State St., Columbus 15, Executive Secretary.

Oklahoma State Medical Association, Oklahoma City, May 1-4. Mr. R. H. Graham, 601 N. W. Expressway, Oklahoma City, Okla., Executive Secretary.

Rare Earths in Biochemical and Medical Research Conference, Iowa State University, Ames, Iowa, May 11-13. J. G. Graca, Ph.D., College of Veterinary Medicine, I. S. U., Ames, Iowa, Program Chairman.

Rhode Island Medical Society, May 10-11. Dr. Arthur E. Hardy, 2 Post Rd., Warwick 5, R. I., Secretary.

Society of American Bacteriologists, Bellevue-Stratford Hotel, Philadelphia, May 1-5. Dr. E. M. Foster, 311 Bacteriology, U. of Wisconsin, Madison 6, Secretary.

Society of Pediatric Research, New Ocean House, Swampscott, Mass., May 3-5. Dr. Clark D. West, The Children's Hospital, Cincinnati 29, Secretary.

South Carolina Medical Association, Ocean Forest Hotel, Myrtle Beach, May 17-19. Mr. M. L. Meadors, 309 W. Evans St., Florence, S. C., Executive Secretary.

(Continued on page 36)

adult group 21 of 26 were female, or 81% (table 3). Skin purpura as a single complaint was present in 17 children whereas only 7 adults had this as the sole problem. Epistaxis was present in six children, with bleeding into the stool in one instance.

The adult group showed menorrhagia as a significant complaint in six patients and, in fact, two patients were considered to have primary gynecologic problems (cases 40 and 47). One patient had a cerebrovascular accident as the presenting clinical problem. Other complaints were gum-bleeding, hematuria, epistaxis, conjunctival bleeding, and rectal bleeding. Fifteen adults, but only five children, had had symptoms for longer than three months. Symptoms in children varied from one day to 10 months; symptoms in adults had a much wider range with durations as long as 10 years. Physical findings, exclusive of hemorrhagic manifestations, were not striking. A palpable spleen was noted in two adults and in five children.

TABLE 2.—*Clinical Features of Idiopathic Thrombocytopenic Purpura in Adults*

Case No.	Sex	Age, Yr.	Major Complaint	Duration of Illness	Hemoglobin Level, Gm. %	Platelets per Cu. Mm.	Physical Findings	Therapy
25..........	F	44	Bleeding, purpura, "stroke"	7 yr.	5.2	0	Coma, CVA, purpura	Steroids, blood (2 units)
26..........	F	62	Skin purpura	2½ mo.	12.8	1,000	Petechiae, purpura, + stool	Steroids, blood (15 units), splenectomy
27..........	M	20	Purpura, rectal bleeding	17 yr.	16.7	72,000	Purpura, + stool	Splenectomy, steroids (seen 3 years postsplenectomy)
28..........	M	52	Leg purpura	5 yr.	15.9	15,000	Purpura	Steroids, splenectomy, blood (1 unit)
29..........	F	76	Bleeding, skin purpura	1 wk.	11.8	5,000	Purpura, eye hemorrhages	Steroids, plasma (2 units)
30..........	F	48	Purpura, bleeding	4 days	6.5	2,000	Petechiae, tarry stool, gum bleeding	Steroids, blood (9 units), splenectomy
31..........	F	38	Bleeding, postoperative purpura	Several yr.	12.5 (postoperative)	11,000	Wound bleeding, purpura	Steroids, blood (6 units), splenectomy
32..........	M	17	Gum bleeding	6 days	13.5	0	Skin purpura	Steroids, blood (1 unit)
33..........	F	34	Purpura	14 yr.	13.3	0	Skin purpura	Splenectomy (12 yr. previously), steroids
34..........	F	32	Purpura, menorrhagia, gum bleeding	6 yr.	14.0	41,000	Purpura, spleen palpable	Steroids, splenectomy
35..........	F	25	Skin purpura	3 mo.	13.0	44,000	Purpura	Steroids, splenectomy
36..........	F	53	Purpura, menorrhagia	2 days	14.5	0	Petechiae, ecchymoses	Steroids, splenectomy
37..........	F	28	Purpura, gum bleeding	3 days	13.4	0	Bleeding gums, hematomas	Steroids, splenectomy
38..........	F	23	Easy bruising	4 wk.	13.7	49,000	Skin purpura	Steroids
39..........	M	59	Purpura, hematuria	2 yr.	13.9	105,000	Purpura, palpable spleen	Steroids, splenectomy
40..........	F	30	Menorrhagia, purpura	3 yr.	10.0	26,000	Petechiae, spleen palpable	Steroids, splenectomy, blood (10 units)
41..........	F	26	Menorrhagia, purpura	8 wk. ? yr.	9.0	20,000	Petechiae	Splenectomy, blood (2 units)
42..........	F	21	Purpura	9 mo.	13.5	69,000	Petechiae	Steroids, splenectomy
43..........	F	54	Purpura, eye hemorrhage	6 mo.	13.5	5,000	Ecchymoses, retinal hemorrhage	Steroids, splenectomy, blood (9 units)
44..........	F	20	Epistaxis, purpura, gum bleeding	10 days	9.5	4,000	Ecchymoses, bleeding gums	Steroids, blood (1 unit)
45..........	F	29	Purpura, gum and nose bleeding	4½ mo.	9.0	0	Petechiae, ecchymoses	Steroids, splenectomy, blood (15 units)
46..........	F	23	Purpura, eye and throat bleeding	8 days	12.5	17,000	Purpura, conjunctival gum bleeding	Steroids, blood (3 units)
47..........	F	16	Menorrhagia	9 yr.	14.0	40,000	Purpura, vaginal bleeding	Splenectomy, blood (3 units)
48..........	F	39	Purpura, easy bruising	10 yr.	11.0	119,000	Petechiae	None
49..........	M	63	Petechiae, bullous lesions	24 hr.	10.0	0	Ecchymoses; blood in stool; bullae in mouth	Steroids, blood (2 units)
50..........	F	17	Menorrhagia, epistaxis	1 yr.	10.5	218,000 (3 yr. after splenectomy)	Vaginal bleeding	Splenectomy

In general, in this series, there is a definite clinical difference in this disease, depending on the age of the patient. Children are more likely to have an acute form of the disease, with symptoms largely restricted to skin purpura, and the sex incidence is quite different, in that ITP is much more common in female than in male adults.

Therapeutic Measures

The therapeutic measures which we have used are, basically, platelet transfusion, administration of steroids, and splenectomy. Platelets have been given either as fresh whole blood or fresh plasma in plastic bags. In the presence of active bleeding or when purpura seems to be particularly severe, and especially as a preoperative or operative measure to prevent surgical bleeding, we have found these transfusions to be of great value. Twenty-two of the 50 patients were given fresh blood or plasma; 7 of these required five or more units.

The experience with steroids in this group of patients is in agreement with previous observations concerning the rapid cessation of or diminution in purpura that takes place when therapy is instituted, either preceding the rise in number of platelets or in the absence of a platelet increase.[5] This has been cytopenic purpuras. Physical examination is performed with attention to adenopathy, hepatomegaly, and splenomegaly, which are unusual findings in the idiopathic variety of ITP.

Laboratory studies include complete blood counts, reticulocyte counts, and usually tests for clot retraction, bleeding time, tourniquet tests, and often the prothrombin consumption test, since these are the usual abnormalities in thrombopenic disease. Platelet counts are performed with use of the indirect cresyl-blue slide technique. Normal values with this test are usually 400,000 to 800,000 platelets per cubic millimeter, in our laboratory. Purpura usually is manifest when counts are in the range of 80,000 or lower, although occasionally purpura is seen with slightly higher values. We have studied liver function in many of the adult patients and routine preparations for the diagnosis of lupus erythematosus are obtained. We have had some experience with platelet agglutinins as part of the initial work-up and we have studied a number of these patients after therapy. These results will be discussed subsequently.

Table 1.—*Clinical Features of Idiopathic Thrombocytopenic Purpura in Children*

Case No.	Sex	Age, Yr.	Major Complaint	Duration of Illness	Hemoglobin Level, Gm. %	Platelets per Cu. Mm.	Physical Findings	Therapy
1	F	2	Skin purpura	2 days	12.0	5,000	Petechiae	Steroids
2	M	3½	Purpura, epistaxis	1 wk.	12.5	10,000	Ecchymoses	Steroids
3	M	7½	Skin purpura	3 wk.	11.4	30,000	Purpura	Blood, splenectomy, steroids
4	M	2½	Skin purpura	2 mo.	12.8	32,000	Purpura; splenomegaly	Steroids
5	F	6	Skin purpura	1 day	13.6	12,000	Purpura; splenomegaly	Steroids
6	F	6	Skin purpura	3 mo.	12.6	84,000	Purpura	Steroids
7	F	14	Skin purpura	10 mo.	13.0	86,000	Purpura	Steroids, splenectomy
8	F	7	Purpura, epistaxis, gum bleeding	2 wk.	11.0	12,000	Purpura	Blood (5 units), steroids
9	F	6½	Purpura	2 wk.	11.5	6,000	Liver and spleen palpable; purpura	Steroids
10	M	6	Purpura, hematomata	4 wk.	12.4	44,000	Purpura; hematomas	Steroids
11	M	7	Skin purpura	6 days	12.8	0	Petechiae	Steroids
12	F	1½	Skin purpura	1 day	9.5	19,000	Petechiae; ecchymoses	Steroids
13	M	11	Skin purpura	6 mo.	15.0	51,000	Purpura	Blood (one unit), splenectomy
14	M	1	Skin purpura	2 days	9.5	10,000	Petechiae; ecchymoses	Steroids
15	M	2	Skin purpura	1 wk.	11.5	10,000	Petechiae; ecchymoses	Steroids
16	M	2½	Skin purpura	2 wk.	11.4	37,000	Skin purpura	Steroids
17	M	10	Skin purpura, bleeding in stool	8 mo.	12.2	8,700	Palpable liver and spleen, purpura	Steroids, splenectomy, bloo (3 units)
18	F	3	Purpura, epistaxis	8 mo.	12.0	67,000	Petechiae	Steroids, splenectomy, bloc (1 unit)
19	M	4	Epistaxis, purpura	2 yr.	8.5	3,000	Purpura; palpable liver and spleen	Steroids, blood (2 units)
20	M	5	Skin purpura	4 days	12.2	6,000	None	Steroids
21	F	5	Purpura, epistaxis	1 wk.	11.0	84,000	Ecchymoses	Steroids, blood (1 unit)
22	F	2	Purpura, epistaxis	2 days	4.3	19,000	Nasal bleeding; purpura	Steroids, blood (2 units)
23	M	7	Skin purpura	2 days	13.0	18,000	Ecchymoses; petechiae	Steroids
24	F	7	Skin purpura	4 days	14.5	5,000	Purpura; pharyngeal bleeding	Steroids

We consider the marrow study to be one of the cornerstones in diagnosis. Use of the marrow-particle technique[2] is considered essential for evaluation of megakaryocytes. We regard either a normal marrow pattern or one showing megakaryocytic hyperplasia as necessary to the diagnosis of idiopathic thrombocytopenic purpura. By "normal" we refer to the presence of a normal granulocytic, erythrocytic, and megakaryocytic series. Specific megakaryocyte abnormalities, namely failure of platelet formation in the megakaryocyte and changes in appearance of the nuclei and cytoplasm of the megakaryocyte, have been described in ITP.[3] It is our opinion that these abnormalities are not specific for ITP and that the only condition which must be met for this diagnosis is a marrow within normal limits or one which shows an increase in the megakaryocytic series.

Marrow samples were obtained in 46 of this series of 50 patients. The most frequent marrow pattern observed was one of megakaryocytic hyperplasia. Occasionally, erythrocytic hyperplasia was seen in those patients who were bleeding. Only one patient who had a hypoplastic marrow initially was studied (case 45). After steroid therapy a sample of marrow was again obtained and found to be normal. T combination of a normal blood cell count wi thrombocytopenia and the marrow picture c scribed, in the absence of a primary disease or citing drug, constitute the criteria for the diagno of ITP in the patients described.

The 50 patients studied included 24 children a 26 adults (tables 1 and 2). The age distribut shows that 72% of all the patients were under years of age, with 42% of the series in the f decade of life (see figure). These figures are unlike Wintrobe's group of patients (81% under years of age).[4] A striking difference is appar when the children are compared to adults (a trarily designated as over 14 years of age). Of children, 11, or 46%, were female, whereas of

An analysis of the group treated with splenectomy (tables 3 and 4) shows more complicated therapeutic problems since, generally, this was the group in which a poor response to steroids was obtained, or in which relapses occurred. In comparison with the steroid-treated group, it can be seen that of 23 patients, only 5 were children. Of the five children who were treated surgically, all had had their disease for seven months or longer. Of the adults in this group, only five had had their disease for less than three months prior to splenectomy. Seventeen patients received steroids as initial therapy. The drugs used were the various steroids, usually different ones in sequence, in an attempt to elicit a platelet response. Twelve patients showed no response to therapy over periods ranging from 1 to 13 weeks.

Five patients relapsed after steroid therapy and were treated again, with temporary remission obtained in two. Relapses occurred at periods varying from nine days to six months after therapy was stopped. A platelet response to splenectomy occurred within 24 hours after operation in 16 patients. Three patients responded in less than one week. We have noted a partial drop in the number of platelets to be a rather frequent occurrence as treatment with steroids is discontinued postoperatively. This is often transient and sometimes reverses without having the drug dosage raised. Occasionally a short period of increased dosage of steroid is necessary. Relapses after splenectomy occurred in nine patients. Five of these relapses occurred less than one month after splenectomy. One patient was seen 13 years after splenectomy with purpura and a low platelet count.

A most interesting feature in this series concerns these nine patients who relapsed after splenectomy and were again treated with steroids. Six recovered and required no further treatment. One patient maintained a normal platelet count with high doses of steroids but required small daily doses of cortisone (12.5 to 25.0 mg. daily) to maintain a partial platelet remission. One patient relapsed 12 days after surgery and despite repeated steroid therapy no response was obtained. This patient (case 39) and one other (case 26) have therapeutic failures, although both are ambulant on maintenance doses of steroids. Thus, of 23 splenectomized patients, there were no deaths, 1 partial remission requiring maintenance medication, and 2 failures.

Complications in the splenectomized patients were infrequent. Pneumonia occurred in one patient. Two patients developed phlebitis and one unusual complication occurred (case 31), in the only patient to have transthoracic splenectomy in this series. One year after splenectomy the patient was admitted with a herniation of the stomach into the chest cavity. This required emergency gastrectomy because of gangrene of the stomach. Recently, we have encountered two patients with complications of splenectomy which are not included in this series. Both patients (one with ITP and one with malignant lymphoma) presented with pleural effusions. In one instance empyema was present. Both patients were found to have a subphrenic abscess. It is well to emphasize that development of significant pleural effusion, in a postsplenectomy patient after the immediate postoperative period is over, should suggest the diagnosis of subdiaphragmatic abscess.

Table 4 summarizes the data in this series of patients. Of 47 patients on whom follow-up data are available, it can be seen that 42 were in complete remission when they were last seen, which in 30 patients was over one year. There was one death, and two additional patients are considered to have therapeutic failures, although both are living, more than one year after splenectomy. Two patients were considered to have partial remissions, and one of these requires maintenance therapy.

Report of Cases

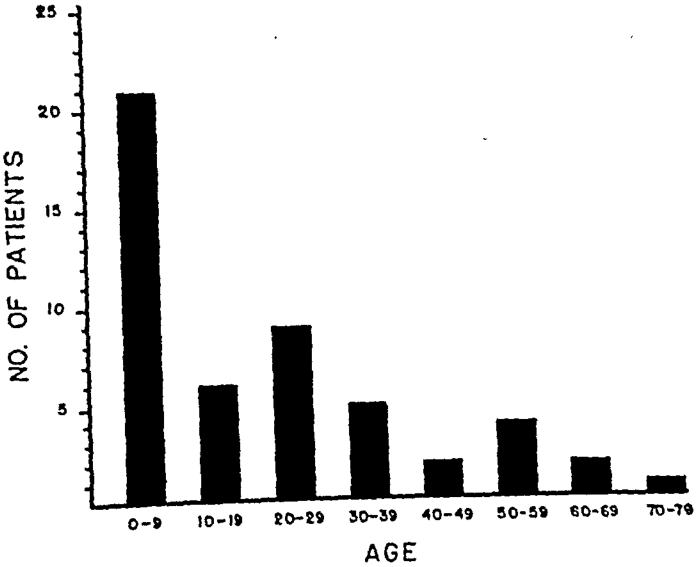
Case 4.—A 2½-year-old boy was admitted to the Albany Hospital on July 31, 1953, with a history of easy bruising of two months' duration. There was no known drug exposure or recent illness. Physical examination revealed purpuric spots over the abdomen, chest, and both lower extremities. The spleen was just palpable. Laboratory data included a platelet count of 32,000 per cubic millimeter, normal white blood cell count and differential count, normal prothrombin time, and positive tourniquet test. Marrow was normal except for megakaryocytic hyperplasia. Cortisone was given, 37.5 mg., four times daily, beginning on July 31. On Aug. 15 the number of platelets was 408,000, at which time the dosage was gradually reduced to 12.5 mg., twice daily. This was discontinued within two weeks. On Nov. 27, the platelet count was normal. The patient was reexamined in July, 1958, five years later, at which time he was well clinically and showed a normal platelet count (over 1 million platelets per cubic millimeter), normal blood values, and a negative result from a lupus preparation.

Table 4.—*Summary of Therapeutic Results*

	Steroids Only				Steroids plus Other Therapy			Splenectomy		Total
Years of Follow-up	<1	1-3	3-5	5-10	<1	1-3	3-5	5-10	>10	47
Complete remissions	7	5	7	4	5	3	5	5	1	42
Partial remissions	..	..	..	..	..	..	1	1	..	2
Failures	1	..	..	..	2	..	..	..	..	3
Relapses after steroid therapy	5	..	..	..	5	..	..	..	..	10
Relapses after splenectomy	..	..	..	..	8	..	..	..	1	9

This patient's course is typical of the uncomplicated case of ITP as seen in children. A rapid response to therapy usually occurs and the child remains well.

attributed to the effect of these drugs on the vascular system.[6] The dosage used for the various agents is somewhat variable. In general, maximum dosage is administered initially. For corticotropin this has been 80 to 100 units, for cortisone, 200 to 300 mg., and for prednisone, 40 to 80 mg., daily, in divided doses. The newer steroids, methylprednisolone and triamcinolone, have not been used in this series. Our impression in patients treated recently is that they have similar therapeutic effects.



Age distribution of patients with ITP. Note preponderance of patients under 30 years of age.

With regard to splenectomy, a significant feature emerges. In no instance in this group of patients was emergency splenectomy performed. The combination of platelet transfusions and steroids in all instances changes an emergency situation into one in which observation and further therapy may be initiated. This prevails, independent of the eventual outcome with a particular patient. In general, splenectomy has been performed on patients receiving steroids (16 patients). The drug is given parenterally preoperatively, during operation, and after operation in maximum doses. Occasionally hydrocortisone is given intravenously immediately prior to and during surgery. Therapy has been continued for 7 to 10 days postoperatively in gradually tapered dosage, provided the platelet count rises. Bleeding as a surgical complication has been practically nonexistent. Only in one patient (case 26, one of the therapeutic failures) did bleeding occur, and this was incisional bleeding which required therapy with large doses of steroids and 15 units of fresh blood for control. All splenectomies were performed infradiaphragmatically except in one case (case 31), in which it was performed transthoracically. Most of the splenectomies were performed by one surgeon with extensive experience with this procedure.[7]

An analysis of the patients in this study is divided into two groups. These are (1) patients who received medical therapy, either no specific treatment or steroids and fresh blood, and (2) the surgically treated group, e. g., those who were splenectomized with or without administration of steroids. This is admittedly an arbitrary division, but it is convenient for analysis. Further, splenectomy is performed only in those patients who respond poorly to medical therapy.

The medically treated group consists of 27 patients. Two of these patients received no treatment and remission was spontaneous. Of the entire group 19 were children and 8 were adults. Of the 19 children only 2 had symptoms for three months or longer, and only 1 of these 2 children was successfully treated with steroids (case 19). Of the eight adults in this group, only two patients had symptoms lasting longer than three months (cases 44 and 48). One patient died within a short time and the progress of the other was inadequately followed. Thus, in the medically treated group only four patients had their disease for over three months, and these can be designated "chronic" if one chooses to accept this period as the dividing line between "acute" and "chronic" ITP. In no instance did an adult with "chronic" disease achieve a satisfactory result with steroid treatment alone.

Cortisone and prednisone were the drugs used most often. In one instance (case 9) no platelet increase occurred with cortisone therapy after nine days, but a response occurred after ACTH was given. This is the only instance in this group in which one particular drug might be said to have an advantage over any other, but this is certainly open to question. Platelet responses usually occurred within two weeks of initiation of therapy, with occasional patients responding in three to four weeks.

There were five relapses and these all occurred within three weeks. There was one death in this group. It occurred in a 44-year-old woman with a seven-year history of purpura. This patient was admitted with an extensive cerebral hemorrhage and died within 24 hours. Three patients have been lost to follow-up but of the remaining group adequate blood studies and follow-up data were available as indicated in table 4. Of 24 patients on whom follow-up studies were available, 23 had had complete remission when they were last seen. Complications from therapy were not significant. In no patient was maintenance therapy required.

TABLE 3.—*Summary of Clinical Features of Idiopathic Thrombocytopenic Purpura*

Patient Data	Children	Adults
Total	24	26
Female	11	21
Symptoms longer than 3 months	5	15
Purpura only	17	7
Splenectomy	5	18
Therapeutic failures	...	3

June 6 and later on the day of operation the platelet count was 221,000 per cubic millimeter. Six days postoperatively the platelet count was normal. The patient was given 4 units of fresh blood in plastic bags preceding and during operation. Administration of ACTH was gradually discontinued within six days after operation. The platelet count remained normal on periodic visits and no further therapy was required. She was seen last five and one-half years after splenectomy, at which time the platelet count was normal and the result of the L. E. cell test was negative.

This case illustrates "chronic" ITP in an adult. A brief course of steroids was ineffectual in elevating the platelet count. Splenectomy resulted in a prompt platelet response without further therapy. It is interesting to note that the presenting problem in this woman was menorrhagia and that her case was initially studied as a gynecologic problem.

Case 36.—A 53-year-old woman was admitted to the Albany Hospital on July 20, 1957, because of diffuse skin purpura of two days' duration. Examination showed diffuse petechiae and a moderate number of ecchymoses on both legs. A small thyroid nodule was palpable, as was the liver edge. Laboratory data showed a platelet count of 0, with all other blood values normal; bleeding time was 11.5 minutes; and result of the L. E. cell test was negative. The marrow showed megakaryocytic hyperplasia. Therapy with prednisone, 80 mg. daily, was initiated, without effect on the platelet count after nine days. On July 29 splenectomy was performed without incident. Within 24 hours the platelet count was 602,000 per cubic millimeter. Administration of steroids was discontinued 12 days postoperatively. On Aug. 3 the platelet count was 3 million per cubic millimeter, and phlebitis occurred which responded, without complication, to anticoagulant therapy. She was discharged from the hospital on Aug. 27. She was seen again 37 days after operation, at which time the platelet count was 12,000 per cubic millimeter. Treatment with prednisone, 60 mg. daily, was begun and the patient was rehospitalized on Sept. 17. Prednisone dosage was raised to 80 mg. daily, and after 10 days 300 mg. of cortisone daily was substituted. Contrast medium (Thorotrast) studies revealed no accessory spleen. ACTH, 80 units daily, was started on Sept. 25 and the cortisone therapy was gradually discontinued. On Oct. 3 (eight days after treatment with ACTH was begun) the platelet count was 423,000 per cubic millimeter. ACTH therapy was gradually decreased and finally stopped on Nov. 8. Since that time the platelet count has been normal. The patient was last seen June 27, 1958, at which time the result of the L. E. cell test was negative.

This patient illustrates again the unpredictability of this disease, particularly in adults, although "acute" steroid therapy did not effect a remission. Further relapse occurred after splenectomy and did not respond to treatment with prednisone or cortisone but did respond to ACTH.

Case 26.—The case of a 59-year-old woman was studied because of skin purpura of four months' duration. Examination showed extensive generalized ecchymoses with hemorrhages in both conjunctivae and in the mucous membranes of the mouth. The spleen and liver were not enlarged. Laboratory tests showed number of platelets 0, remaining blood values normal; bleeding time 14 minutes; prothrombin consumption abnormal (13 seconds), clot retraction abnormal; result of tourniquet test positive; and result of L. E. test negative. The marrow was normal except for megakaryocytic hyperplasia. Therapy consisting of 80 units of ACTH daily for four days and prednisone, 60 mg. daily for 10 days, effected no platelet response.

Splenectomy was performed 16 days after admission. The wound healed poorly and bled copiously, necessitating 15 fresh blood transfusions within 12 days after operation. Therapy with varying steroids, ACTH, cortisone, and prednisone, was tried without a platelet response. The patient was discharged two months after entry to the hospital with only slight purpura. The wound had healed prior to discharge. Her progress as an outpatient was subsequently followed; at this time she was taking 4 to 8 mg. of methylprednisolone daily. She had some leg purpura but no frank bleeding, and the platelet count fluctuated between 30,000 and 120,000 per cubic millimeter. Eighteen months after splenectomy she was rehospitalized and a two weeks' course of ACTH was given to no avail. At present she is working and is maintained on 4 mg. of methylprednisolone daily.

This patient represents a therapeutic failure. Although the platelet count is markedly reduced, the combination of splenectomy and steroids has produced some diminution in the purpura, permitting this patient to work. The difficult problem of bleeding postoperatively when a good platelet response does not occur is demonstrated in this case.

Comment

Several authors in the past have reviewed large series of patients with ITP.[8] Attempts have been made to classify or group the patients in such a fashion as to be able to predict the outcome in an individual case. The major groupings in these reports have been ITP in children as opposed to adults and "chronic" as compared to "acute" ITP. The attempt made by these classifications is a valid one in that the indications for and timing of splenectomy constitute major problems in the management of the patient with this disorder. Wintrobe,[4] in 1937, reviewed the cases of 62 patients, of whom 64.5% were under 12 years of age. Nineteen of these patients were splenectomized. Eighteen patients

Case 24.—A 7-year-old girl was admitted to the Albany Hospital, on June 30, 1955. Mumps had been diagnosed one month before entry and was followed in a few days by purpura on her arms, legs, and back. Results of examination were negative except for skin purpura and minor bleeding in the posterior pharynx. Laboratory data showed a platelet count of 4,800 per cubic millimeter; normal hemoglobin value, white blood cell count, and differential count; bleeding time 20 minutes; prothrombin consumption abnormal; clot retraction slight in 24 hours; and results of tourniquet test strongly positive. The marrow was normal except for megakaryocytic hyperplasia, with an increase in immature forms. Administration of cortisone was begun, 100 mg. twice daily. The platelet count was normal 15 days later, and the drug therapy was discontinued slowly. Six days after therapy had been discontinued the number of platelets had fallen to 40,000 per cubic millimeter. Therapy with prednisone was reinstituted, 30 mg., daily for two days, then reduced to 20 mg., daily. The number of platelets was 350,000 per cubic millimeter three days later. Treatment with prednisone, 15 mg., daily, was continued for three weeks and then discontinued. Fifteen days later the platelet count was 90,000 per cubic millimeter. Prednisone therapy was reestablished at a dosage of 20 mg. daily and reduced to 10 mg. daily in three weeks. The platelet count was 335,000 per cubic millimeter after three days of therapy. One month later all therapy was discontinued. There were no further relapses at interval visits and in July, 1958, three years later, the number of platelets was 768,000 per cubic millimeter, the blood count was normal, and the child was asymptomatic.

This case illustrates the unpredictability of therapeutic response in any given patient. Two relapses occurred, both requiring steroid therapy, but complete remission three years after treatment has been maintained. The onset of ITP after an acute illness, in this instance mumps, is not uncommon in children.

Case 3.—A 7½-year-old boy was seen because of skin purpura of three weeks' duration. Physical examination revealed negative findings except for diffuse skin petechiae and small ecchymoses. Laboratory data showed platelets, 29,000 per cubic millimeter, hemoglobin level 11.4 Gm.%, and white blood cell and differential counts normal. The marrow was normal except for erythrocytic and megakaryocytic hyperplasia. The patient was treated with cortisone, starting with 200 mg. daily, and 17 days later the number of platelets was normal. Eleven days after cessation of therapy the number of platelets was 147,000 per cubic millimeter. Over a period of five months cortisone, in varying doses, was given on an outpatient basis without achieving a normal platelet count. Six months after he was first seen the platelet count was 14,000 per cubic millimeter and splenectomy was performed. The platelet count then promptly rose to 700,000 per cubic millimeter. Eleven months after splenectomy relapse again occurred and prednisone therapy, 60 mg. per day, was started. The platelet count was normal in one week and over a period of four weeks the drug was discontinued. This boy was last seen seven months after his last course of therapy, at which time his platelet count was normal.

This case illustrates an initially responsive child who subsequently relapsed and required splenectomy after a failure to respond to steroid therapy. Further relapse occurred after splenectomy, but the patient again responded to treatment with steroids.

Case 46.—A 23-year-old woman was admitted to the hospital because of purpura of the legs and body of eight days' duration. Ten days prior to the onset of symptoms she was diagnosed as having rubella. Shortly before entry minor epistaxis and hematuria had occurred. Physical examination revealed negative findings except for purpura. Laboratory data showed normal hemoglobin value white blood cell count, and differential count. The platelet count was 17,000 per cubic millimeter bleeding time was over 12 minutes and the resul of the tourniquet test was strongly positive; the marrow was normal except for megakaryocytic hyperplasia. She was started on therapy with cortisone, 200 mg. daily. The platelet count was normal 11 days after the onset of therapy. The drug therapy was gradually decreased until the time of discharge, 16 days after admission. The patient has since been asymptomatic, and when seen five and one-half years later the platelet count was normal and the result of the L. E. test was negative.

This case represents the acute form of ITP in an adult which, in this series, is not common. The patient's response was satisfactory to one course of steroids.

Case 40.—A 30-year-old woman was admitted to the gynecology service of the Albany Hospital on May 22, 1952, because of menorrhagia of two years duration. In 1951, when she had a salpingo-oophorectomy, 11 transfusions were required. She had bruised easily for about three years. Findings of physical examination were unremarkable except for diffuse petechiae over the legs and trunk; the spleen was just palpable. Laboratory studies showed a platelet count of 26,000 per cubic millimete normal white blood cell and differential counts, hemoglobin concentration, 10 Gm.%, bleeding time 6.5 minutes, clot retraction absent, plasma recalcification time six minutes (normal: under two minutes), results of direct Coombs test, positive. Study showed megakaryocytic hyperplasia in an otherwise normal marrow. ACTH, 100 units daily, was started on June 2, without appreciable effect on the platelet count. The patient was splenectomized on negligible. Regardless of age, the chronic form of the disease is much less likely to respond to steroid therapy, particularly if a response is not obtained within two to three weeks. This knowledge aids in planning therapy. Again, in view of the tendency of the disease to relapse, hard and fast rules cannot be applied.

We have inadequate information to compare the various steroids in our group of patients. In two patients, however, we have seen ACTH effect a response when the other steroids failed. We have summarized our experience in all patients receiving steroid therapy in table 5. In this group of 41 patients 21 were children. Permanent remission occurred in 18 patients with one course of therapy; 13 of these were children. Four patients relapsed and obtained complete remission with an additional course of therapy; three of these patients were children. Seventeen patients were splenectomized, after a failure to respond, or after relapse; five of these patients were children. One death occurred within 24 hours after admission, as has been previously described, and one child was lost to follow-up after failing to respond after 40 days' therapy. None of these patients showing complete remission required maintenance therapy.

Attention has been called recently to the high incidence of lupus erythematosus in patients with ITP,[13] particularly in splenectomized women. An incidence of 15.2% is reported in a series of 51 consecutive cases of ITP, with an additional 15% in this group of patients showing several of the features of lupus. We have been able to restudy 32 patients (table 6) and have found negative results of L. E. cell tests and no clinical evidence to suggest lupus in any of these patients. We have also asked a member of our pathology department to reevaluate the spleens removed surgically. In no instance were anatomic findings suggesting lupus found. A recent review of a large series of patients with lupus reports two instances of thrombocytopenic purpura.[14]

Table 5.—*Results in Forty-one Patients with Steroids as Initial Therapy*

Result	Follow-up, Yr.				Total
	<1	1-3	3-5	5-10	
Permanent remission (one course)	7	2	4	5	18 13 child.
Permanent remission (re-treated)	1	...	3	...	4 3 child.
Splenectomized	5	5	4	3	17 5 child.
Failures	2*	...	...	...	2

* One patient died within 24 hrs.; one patient lost to follow-up (40 days).

Platelet agglutinins have also been studied in 29 patients as part of our follow-up study and evaluation (table 6). We have used a modification of Harrington's technique.[15] Results were weakly positive in nine patients and positive in four. The results in the rest were negative. This series is much too small for any true evaluation, but no relationship is found relative to splenectomy or relapse. The two patients who had therapeutic failures had results of tests described as weakly positive.

Table 6.—*Follow-up Study—L. E. Cell Test Results and Platelet Agglutinins*

Result	Follow-up, Yr.				Total
	<1	1-5	5-10	>10	
Platelet agglutinins					
Negative	2	9	5	...	16
Weakly positive	1	7	1	...	9
Positive	...	1	3	...	4
Negative result of L. E. cell test	4	17	10	1	32

Summary and Conclusions

Fifty cases of idiopathic thrombocytopenic purpura are described, with their management and eventual outcome. The combined use of fresh blood or platelet transfusions, steroids, and splenectomy produced satisfactory over-all results. There were two therapeutic failures, and only one death, in the entire series. No deaths occurred as a result of splenectomy. It was not necessary to perform emergency splenectomy in any instance. Stringent rules for the management of the individual patient with ITP cannot be supplied, because of the incidence of relapses and the unpredictability of this disease.

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Dr. Arthur Stein, professor of pathology, Miss Vivian Dylong, research technician in hematology, and Mr. Richard Propp, medical student, assisted in the preparation of this study.

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relapsed, with relapses occurring many years after the first episode of purpura. Twenty-five patients had one episode only. Included in this study was a combined clinic group in which 54 patients were treated medically, with 2 deaths; of 24 having splenectomies there were 5 deaths. Splenectomized patients showed permanent recovery in about 75% of the cases, whereas medical therapy produced recovery in about one-third. Wintrobe concluded that the "acute" and "chronic" differential should not be applied rigidly to the outcome of an individual case, because an acute situation may become chronic, and further that the incidence of relapses makes this disease extremely unpredictable.

Hirsch and Dameshek, in 1951,[8a] studied 89 patients with ITP. They attempted to divide the group into those with an acute, self-limited form of the disease (present in 26 patients) and those with a chronic form (present in 55 patients); however 8 patients were unclassified. There were eight deaths in the entire series. The patients were grouped as "acute" if the duration of the disease was less than four months and was associated with an abrupt onset, often allergic, and with marrow eosinophilia and lymphocytosis. Of 18 patients with proved self-limited disease, 8 were followed up for less than one year and 7 were under 10 years of age. Of 22 "acute" patients, 1 died. Four splenectomized patients in this group died. In the "chronic" form of the disease, 41 of the 52 patients were splenectomized, with three deaths; 22 patients were followed up for less than six months. Splenectomy resulted in recovery in 63%.

The conclusion of the authors was that there is a group of patients with ITP which should be designated "acute" and self-limited and who spontaneously improve in a period of four months or less. A second group, with the "chronic" disease, is expected to do well with splenectomy in about two-thirds of the cases. Lozner's summary of 303 splenectomies[8b] confirms these figures. The mortality in Lozner's collected cases was 11%, with 61% with complete remission and 17% with incomplete remission. Lozner[9] and Stefanini[1] agree that the appearance of the marrow offers little prognostically and in this we concur.

Our patients, when subdivided in a similar fashion, show the following comparative results. Of 24 children, only 5 were splenectomized, and these 5 children had all had their disease for more than seven months. Three of these splenectomized children did not respond initially to treatment with steroids (for 6 days, 18 days, and three months), and two relapsed after steroid therapy. The rest responded to treatment in 4 to 28 days. One child responded to steroid therapy who could be considered "chronic." Of the 26 adults, only eight patients did not eventually undergo splenectomy. Six of these eight patients, on whom data were available, responded to medical therapy in under 17 days, with normal platelet counts. None of these patients could be classified as "chronic." Of the adults who had splenectomies, only four would be designated "acute." Three of these patients failed to respond to steroid therapy in 31, 9, and 9 days respectively. Our splenectomy results compare favorably with previous groups,[8] but it should be pointed out that earlier studies do not include conjunctive steroid therapy. Splenectomy resulted in complete remission in 82.6%, with two failures, two partial remissions, and no mortality. All the patients benefited from splenectomy, in that active bleeding stopped and progressive purpura diminished.

Perhaps the most difficult decision to make in a particular patient with ITP is whether splenectomy should be performed. In adults the disease is more often chronic and does not respond readily to medical therapy, whereas in children the disease is more likely to be acute and remission will usually occur in a relatively short time. Whether this is spontaneous or steroid-induced can only be conjectured. An interesting review of ITP in children was reported by Newton and Zuelzer in 1951,[10] the "presteroid era." Forty-seven cases were studied and therapy consisted of giving banked blood only. There were two deaths among four patients who had cerebral bleeding. Seven children were splenectomized. Twenty-nine of 42 patients had spontaneous remissions within one month. It is difficult to evaluate any form of therapy in this group because of spontaneous remission, but the cerebral complications and a definite mortality have been reported without benefit of platelet transfusion and steroid therapy.

A number of reports have appeared concerning steroids and their beneficial effect in ITP.[11] Most recently an article has appeared in which 30 consecutive patients with this disease were treated with prednisone, with good initial platelet responses in 73%.[12] Eleven of these patients were classified as "acute" and 19 as "chronic." Twelve patients were under 20 years of age. Relapses occurred in 7 out of 24 patients. Only eight patients of the entire series, however, did not require maintenance therapy; four of these were "chronic." Five patients were treated before splenectomy and two patients after splenectomy, with variable results. The authors concluded that ITP is a medical disorder and that splenectomy is to be avoided as long as possible.

A decision must be made, however, regarding treatment in a particular patient and the likelihood of remission must be balanced against the risk of splenectomy, the likelihood of cure with surgery, and the potential toxicity of the drugs used. From the series reported in this communication, it would appear that combined therapy renders the mortality either with or without splenectomy practically

Materials and Methods

Bunamiodyl is 3-(3-butyrylamino-2,4,6-triiodophenyl)-2-ethyl sodium acrylate, with the following structural formula:

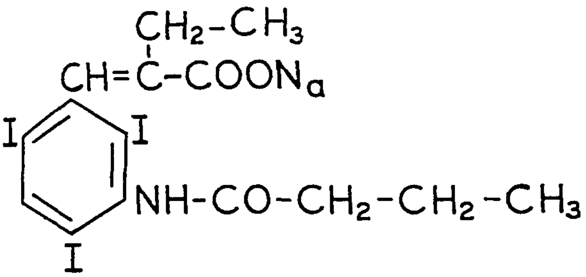

Fig. 1.—Formula of bunamiodyl.

Bunamiodyl is a white, odorless, slightly hygroscopic powder. The melting point is not clear; there is fusion with decomposition between 220 and 230 C. It is somewhat soluble in water and alcohol and is stable under normal conditions of heat and light. Bunamiodyl has a molecular weight of 661 and contains 57% iodine. Table 1 shows the comparative molecular weights and iodine content of bunamiodyl and several other commonly used agents.

Table 1.—*Comparative Data*

	Bunamiodyl	Sodium Tetraiodophenolphthalein	Alpha-Phenyl Propionic Acid	Cyclohexane Carboxylic Acid	Iopanoic Acid	Propionic Acid
Molecular weight	661	682	494	486	571	572
Iodine, %	57.0	58.6	51.5	52.2	66.7	66.5

Table 2.—*Toxicity of Bunamiodyl Compared with Older Mediums**

Medium	Bunamiodyl[4]	Iodoalphionic Acid[5]	Iopanoic Acid[5]
LD_{50}, mg./kg.	570	400	360

* Acute intravenous toxicity studies in mice.

The animal toxicity of bunamiodyl is notably low. Table 2 presents the pertinent data on comparative intravenous toxicity. Although these compounds are given orally, the intravenous route was selected for the determination of the median lethal dose (LD_{50}) because a truer picture of relative toxicity is thus obtained. Poor absorption of a drug from the gastrointestinal tract will result in misleading values, whereas the intravenous administration eliminates any variations due to differences in absorption. Moreover, it is only after absorption that a compound becomes toxic, a further reason to look to intravenous values for the true level of toxicity.

Present Study.—Cholecystography was performed in 500 unselected adult patients referred to the Department of Radiology of Cook County Hospital. A standard oral dose of 4.5 Gm. of bunamiodyl was given to each patient regardless of age or weight. The contrast medium was given in six capsules of 0.75 Gm. each for ingestion on the evening preceding the examination. A liquid fat-free diet was maintained from the time of ingestion of the drug until the procedure was completed on the following day. Although not usually used in our routine cholecystographic procedures, fat meals were given in 50 cases to determine the adequacy of gallbladder emptying and the incidence of duct visualization.

Patients were interrogated before and after the study to determine the incidence and severity of side-reactions. All films were rated for quality of opacification, visualization of gallbladder, and presence of calculi or other pathological findings. The presence or absence of unabsorbed contrast material in the colon was noted and recorded.

Table 3.—*Results—Incidence of Side-Reactions, %*

		Seedorf and Co-workers[6]			
Reaction	Bunamiodyl, 500 Cases	Iopanoic Acid, 100 Cases	Alpha-Phenyl Propionic Acid, 100 Cases	Cyclohexane Carboxylic Acid, 100 Cases	Propionic Acid, 100 Cases
Nausea	14	17	27	28	26
Vomiting	4	1	0	0	4
Diarrhea	4	39	38	13	31
Dysuria	2	29	48	23	36
Cramps	4	29	21	19	25
Rash	1	4	4	7	4

Clinical Results

The amount of iodine ingested and absorbed roughly determines the degree and quality of gallbladder opacification. Heretofore the dosage of triiodinated compounds required to achieve a satisfactory degree of opacification has resulted in a generally high incidence of unpleasant side-reactions, such as nausea, vomiting, diarrhea, dysuria, cramps, and skin reactions.

Butyrylation of the free amine in the molecule of bunamiodyl permits the use of dosages essential for clinically adequate opacification, with a surprisingly low number of side-reactions. In our series, patients' acceptance of bunamiodyl was better than that of

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CHOLECYSTOGRAPHY WITH BUNAMIODYL

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and
Frederick M. Rich, M.D., Chicago

The effectiveness and safety of bunamiodyl, given by mouth for purposes of cholecystography, were studied in 500 patients. Given in a total dose of 4.5 Gm. in six capsules on the evening before the examination, bunamiodyl afforded fair, good, or excellent visualization of the gallbladder in 364 and poor visualization or none in 136 patients. In this dosage it caused nausea in only 14% of patients. In 23 patients whose progress it was possible to follow after the examination, a roentgenographic diagnosis of cholecystitis, cholelithiasis, or both, was confirmed at surgery in every case. Compared with other contrast mediums used, bunamiodyl in the above dosage caused less diarrhea and dysuria. There was also less difficulty with unabsorbed radiopaque residues in the intestine which tend to confuse the reading of the roentgenograms.

The work of Graham and Cole[1] firmly established the feasibility and value of iodinated compounds as contrast agents in cholecystography and the differential diagnosis of gastrointestinal diseases. Since that time, many iodinated compounds have been developed—particularly for oral administration. Each of these has had some advantage over its predecessors, yet none of these has been completely satisfactory in all respects.

The ideal contrast medium for cholecystography should have the following characteristics.[2] (1) absence or low level of systemic toxicity; (2) early and rapid absorption on oral administration, without irritation of the gastrointestinal mucosa; (3) selective excretion in the bile and consequent localization in the gallbladder; (4) high radiopacity of the gallbladder; (5) reliable results after oral administration; and (6) rapid and complete elimination.

A new compound, bunamiodyl (Orabilex), has recently been introduced and a number of investigators have reported on its advantages.[3] This report is concerned with our experience with bunamiodyl in 500 cases in a large county hospital where the conditions and problems encountered are most demanding. Our results indicate that bunamiodyl is a safe and effective cholecystographic agent, with a significantly low incidence of unpleasant side-effects —an important factor, particularly from the patient's viewpoint.

From the Department of Radiology, Cook County Hospital. Presented as a Scientific Exhibit before the Section on Radiology at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 8-12, 1959.

appear in the gallbladder area, may be mistaken for opaque calculi or may mask the gallbladder itself.[7] Intestinal residual, when it occurs with bunamiodyl, has usually been a diffuse staining rather than a discrete density. In our series there was no instance in which the residual matter interfered with diagnosis. Of the 500 cases, residual dye in the colon was seen as minimal to none in 368 (73.6%); moderate in 116 (23.2); and dense in 16 (3.2) (fig. 2, 3, and 4).

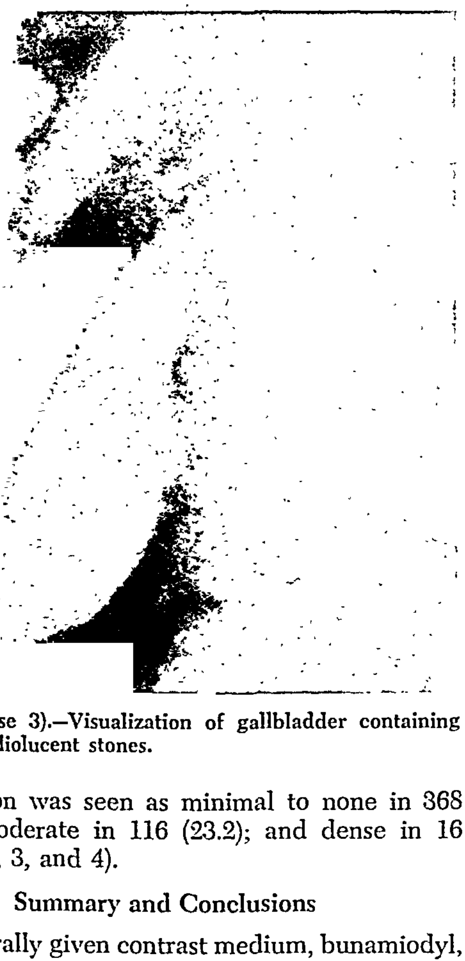

Fig. 4 (case 3).—Visualization of gallbladder containing numerous radiolucent stones.

Summary and Conclusions

A new orally given contrast medium, bunamiodyl, was used in 500 consecutive patients referred for routine cholecystography. The order and severity of side-effects was less than that observed by ourselves and, apparently, by others when compared with several other commonly used contrast agents. The quality and intensity of contrast values with use of a standard six-capsule dose (4.5 Gm.), regardless of patient weight, were satisfactory.

Unabsorbed colonic residual medium, often confusing when other mediums are employed, is minimal with bunamiodyl. If it does occur, it is usually diffuse in character and does not interfere with film interpretation.

On the basis of this evaluation, we believe bunamiodyl to be a safe and efficient orally given cholecystographic contrast medium. Fewer side-effects and some technical improvement over presently used agents were observed.

1853 W. Harrison St. (Dr. Meszaros).

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REACTIONS OF ADULTS TO SEXUAL ACTIVITIES OF CHILDREN.—The severity with which sexual behaviour among children is often regarded by members of the adult population is due to the internal guilt and anxiety, much of it unconscious, that most members of the adult community bear within themselves; and it is related, therefore, in no small measure to their own rather than their children's sexual conflicts. It is largely for this same reason that adults, whether parents or educators, have so often felt inadequate to giving to children the help they need in handling their problems. Nevertheless there are, allied in this field today, many enlightened family doctors, juvenile magistrates, probation officers, leaders in the youth service, marriage counsellors, and parents, and it is becoming increasingly common for dispassionate and understanding attitudes to prevail when sexual misdemeanours come to notice.—D. T. Maclay, M.D., Boys Who Commit Sexual Misdemeanours, *British Medical Journal,* Jan. 16, 1960.

any other contrast material previously used. Table 3 shows our results with bunamiodyl in 500 cases compared to those of Seedorf and co-workers[6] with four other commonly used contrast mediums in 100 cases each.

Of interest to us in our series of patients given bunamiodyl was the low incidence of diarrhea and dysuria—two of the most important reactions encountered in cholecystography. Diarrhea is not usually life-threatening and is often overlooked by the roentgenologist, but it can be most unpleasant and frequently incapacitating to the patient. Dysuria, on the other hand, is not only uncomfortable but may herald potential renal damage. Despite the fact that bunamiodyl is largely excreted in the urine, there is a gratifyingly low incidence of dysuria. Particularly interesting is the fact that less dysuria is seen with bunamiodyl than with iopanoic acid—a compound which is largely excreted intestinally.

Table 4.—*Quality of Opacification*

Result of Examination	Cases No.	Cases %
Visualization		
Excellent to good	290	58
Fair	74	14.8
Poor	34	6.8
Total	398	79.6
Nonvisualization	102	20.4

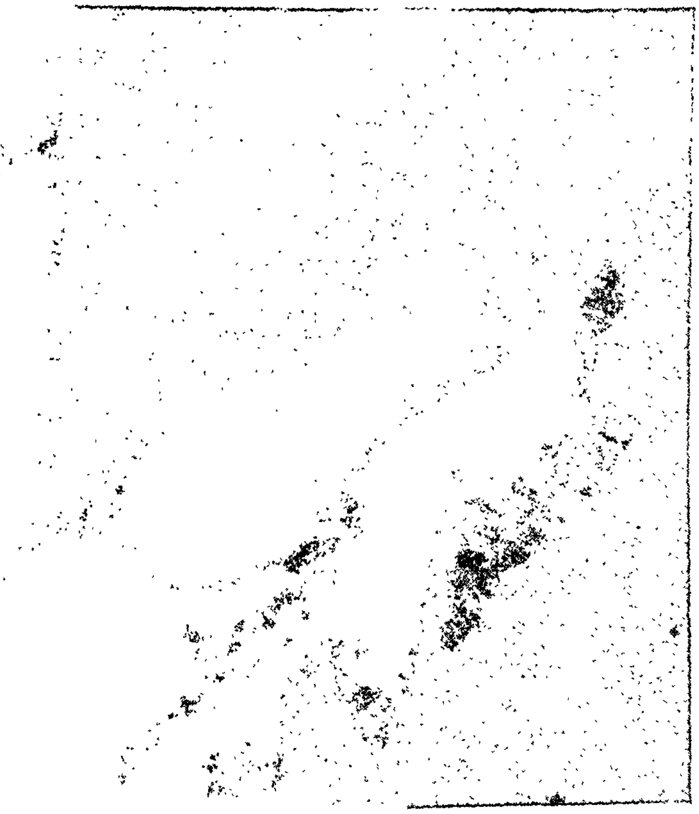


Fig. 2 (case 1).—Excellent visualization of gallbladder after administration of bunamiodyl. Common duct is visualized, although no fatty meal was given.

The quality and degree of opacification in our series were satisfactory. In no cases were radiopaque calculi or other pathological findings obscured or concealed. Radiolucent calculi, when present, were readily discernible and, in many instances, the common and hepatic ducts were prominently delineated. In 23 patients whose progress we were able to follow, a roentgenographic diagnosis of cholecystitis, cholelithiasis, or both, was confirmed at surgery in every case, indicating a high order of reliability for the medium.

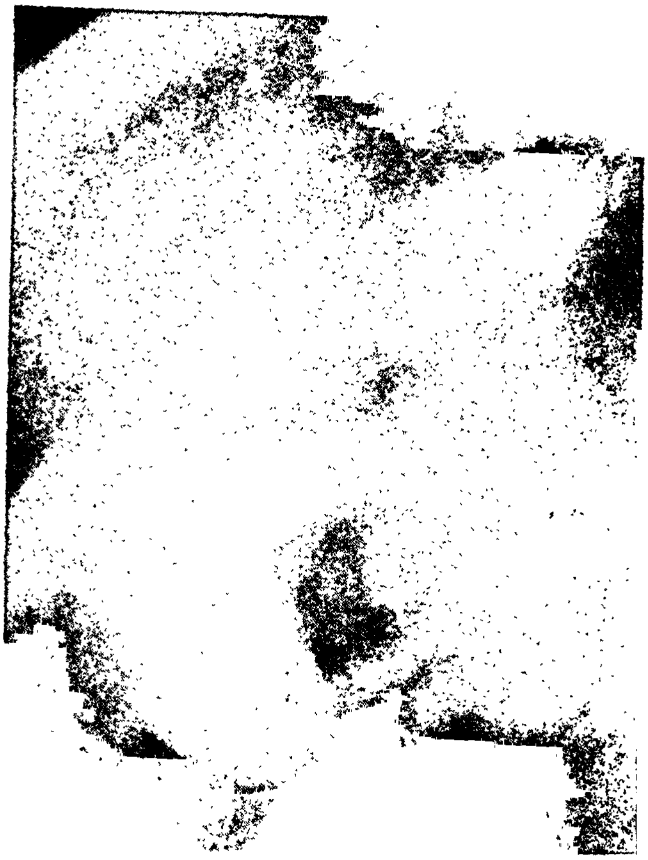


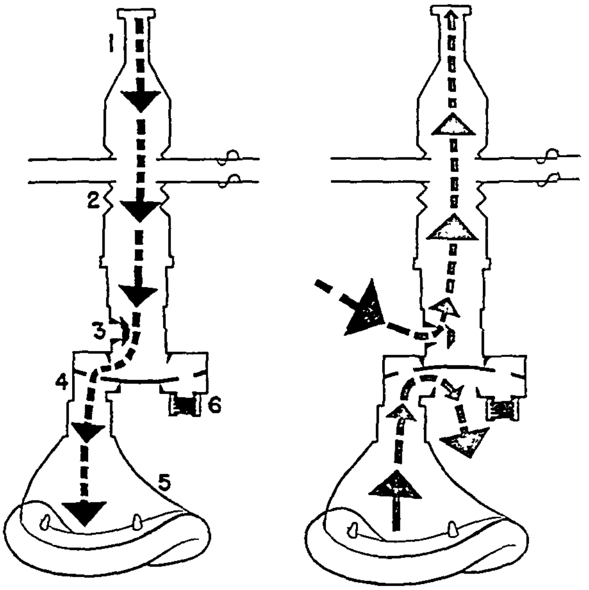
Fig. 3 (case 2).—Bunamiodyl cholecystogram after fatt meal. Clear delineation of gallbladder, cystic duct, an common duct. Note absence of unabsorbed contrast mediu in colon.

Our percentage of nonvisualized cases was hig when compared with results obtained with thi compound by other investigators.[3] We have n valid explanation for our apparently atypical findings. Our patients are drawn from all services of this hospital, including the psychiatric division. No attempt was made in the presence of nonvisualization to determine if the patient received proper dietary preparation for the examination. It is possible that many of our 102 nonvisualized patients were found to have disease on subsequent procedures. The scope of our examination, however, did not encompass follow-up data. We have chosen, nevertheless, to include all data available.

In our series gallbladder contractility was good and bunamiodyl did not in any way interfere with emptying or cause any other disturbance of gallbladder physiology. In the 50 patients to whom fat meals were given, the cystic duct was visualized in every case and the common duct was visualized in 19, or nearly 40%, of the cases. Gallbladder contractility was seen to be good in all patients.

One of the chief disadvantages of iopanoic acid has been the frequent occurrence of intestinal residuals as discrete densities which, when they

Five subjects (table 1), four with restrictive ventilatory insufficiency secondary to chronic poliomyelitis and one undergoing a right upper lobectomy, were studied. Three of the subjects with poliomyelitis used mechanical respiratory aid for most or all of the day; the fourth refused to use respiratory aid and was known to have a mild respiratory acidosis. The other subject had satisfactory respiratory function.



Design of mouth-to-mask resuscitator, showing direction of flow created by operator exhalation and inhalation. Note direction of victim's exhalation. 1. Operator mouthpiece. 2. Breathing tube of 300-cc. capacity. 3. Inlet inhalation valve. 4. Diaphragm controlling flow to victim. 5. Patient mask. 6. Pressure relief valve set for 24 mm. Hg.

TABLE 3.—*Blood-Gas Studies in Patients Before and During Mouth-to-Mask Resuscitation*

	Before Resuscitation														
	Control, During Respiratory Aid or Initial Value				During Unassisted Breathing					During Resuscitation					
Case	PO_2, Mm.Hg	PCO_2, Mm.Hg	pH	CO_2, mM/L	Duration, Min.	PO_2, Mm.Hg	PCO_2, Mm.Hg	pH	CO_2, mM/L	Duration Min.	PO_2, Mm.Hg	PCO_2, Mm.Hg	pH	CO_2, mM/L	Remarks
1.............	102.7	24.5 25.4*	7.51	20.6	6	67.9	39.4 39.2*	7.40	25.1	23	101.3	34.8 33.2*	7.45	23.6	Immediate relief of respiratory distress with resuscitation
2.............	98.0	22.6 24.6*	7.19	19 2	11	78.7	37.0 36.9*	7.38	22.5	21	98.4	32.3 28.6*	7.44	20.0	Same as above
3.............	75.8	49.5 50.9*	7.33	28.0	...	...	...	...	...	13	94.4	39.1 36.2*	7.45	25.7	After 12 min. of resuscitation patient developed symptoms of acute respiratory alkalosis
4.............	90.8	31 3 35.2*	7.42	23.6	...	...	...	...	...	23	92.6	26.6 25.8*	7.49	20.1	...
5.............	84.6	39.0	7.37	...	5	72.3	46.3	7.33	...	5	76.2	39.7	7.37	...	...

* Calculated PCO_2.

An arterial needle was inserted into the brachial artery of all subjects. In two of the patients with poliomyelitis a control sample of blood was obtained while each was receiving respiratory aid. A second sample was obtained after a short period of unassisted breathing and the development of fatigue. In the other two subjects the initial blood was obtained without respiratory aid, with the patients asymptomatic. In all four, blood was drawn after a period of respiratory assistance with the mouth-to-mask unit at a respiratory rate of 16 to 17 per minute. Determinations of oxygen and carbon dioxide tensions (PO_2 and PCO_2) were performed in duplicate by the method of Riley and co-workers.[1] Carbon dioxide content of the plasma was analyzed on the Kopp-Natelson apparatus, and plasma pH was analyzed at 37 C on a model GS Beckman meter with use of the Beckman microcapillary technique as modified by Wheeler and co-workers.[5] A control sample was drawn after preoperative medication on the fifth subject. A second sample was drawn five minutes after administration of curare and thiamylal (Surital) sodium. At this stage respiration was depressed but not completely abolished. The mouth-to-mask resuscitation was begun at a rate of 16 to 20 breaths per minute and a sample was drawn after five minutes.

TABLE 2.—*Mechanical Efficiency of Mouth-to-Mask Resuscitator*

Test Conditions	No. of Determinations	Av. Volume, Cc.		Difference	
		Entering Valve	Leaving Valve	Cc.	%
Tidal volume	12	1,180	1,110	—70	—6
Vital capacity	12	4,390	4,068	—322	—7.3
Varying volumes with weight added to spirometer bell, Gm.					
175....................	6	1,110	1,200	+90	+7.5
385....................	6	1,410	1,480	+70	+5
770....................	6	1,670	1,530	—160	—8
770	6	1,690	1,580	—110	—6

Results

Mechanical Effects.—The results, as shown in table 2, indicate the high degree of efficiency of transfer of air across the valve. The small differ-

MOUTH-TO-MASK RESUSCITATION

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An instrument which circumvents objectionable aspects of mouth-to-mouth contact when this method of resuscitation is used has been devised. A simple nose and mouth mask, a flutter valve, and an outflow valve prevent the flow of expired air from the injured person to the operator. An inflow valve on the operator's side of the flutter valve provides fresh air. The length of the tube allows the operator to first rebreathe 300 cc. of his previously exhaled air and prevents him from hyperventilating. A relief valve opens when ventilation pressures exceed 24 mm. Hg. The mechanical and physiological efficacy was checked by laboratory testing of the exchanged air and of blood samples drawn from five subjects during actual resuscitative conditions. The mouth-to-mask method of artificial respiration proves to be safe, simple, and efficient.

The mouth-to-mouth technique of artificial respiration has been demonstrated and accepted as the most practical method for the emergency ventilation of an apneic person of any age, in the absence of equipment, regardless of the cause of the apnea. Mouth-to-mouth resuscitation has unequivocally been shown to be superior to manual methods and can be extended for long periods of time. During its application one senses resistance and obstruction to breathing and the early return to spontaneous breathing; thus better control is possible than with manual methods.[1]

There are objections, however, to mouth-to-mouth resuscitation, which include (1) a reluctance and apprehension to breathe into an apneic person, the operator fearing infection and contamination; (2) invariable hyperventilation and frequent experiences of dizziness and fatigue resulting in decreased efficiency; (3) reluctance to participate in training programs which teach this method; and (4) a risk of overdistention of the lungs, especially in infants and children.

In order to overcome these objections and still provide an efficient method of ventilating the lungs, mouth-to-mask techniques have been recommended.[2] The following report is an evaluation of this form of resuscitation.

Materials and Methods

A mouth-to-mask unit of the design shown in the figure was used for the study.[3] The first 300 cc. of air or part thereof with which the victim is ventilated is atmospheric, since the operator previously inspired atmospheric air through the tube. Overinflation is prevented by a pressure relief valve, set for 24 mm. Hg. There is no rebreathing of the victim's air by the operator, since he rebreathes the last 300 cc. of his previous exhaled air mixed with atmospheric air coming through the *inlet* valve.

The mechanical efficiency of the mouth-to-mask resuscitator was determined by measuring the volume of air entering and leaving the valve. One end of the valve was attached to a recording spirometer and the other to a gas flow meter, and measurements were made with use of variations of rate and depth of breathing and by the addition of resistance to the spirometer.

The oxygen and carbon dioxide concentrations of the exchanged air breathed by the operator were measured with an oxygen analyzer and an infrared carbon dioxide analyzer. The operator's expired air was collected in a Tissot gasometer and the mean carbon dioxide and oxygen concentrations analyzed. This was done to determine the concentration of these gases which the victim would receive.

Table 1.—*Data on Subjects Tested*

Case	Sex	Age, Yr.	Weight, Lb.	Onset of Disease, Yr.	Vital Capacity, Cc.	GPVC,* Cc.	Continuous Unassisted Breathing Time, Hr.	Disease
1	F	11	62	1958	50	700	1/20	Poliomyelitis
2	F	20	108	1954	150	1,350	½	Poliomyelitis
3	M	17	82	1951	1,050	...	24+	Poliomyelitis
4	F	9	50	1958	325	700	3	Poliomyelitis
5	F	26	135	1957	4,641	...	...	Pulmonary Disease

* Vital capacity with use of glossopharyngeal breathing.

From the Cardiopulmonary Laboratory, Ohio Tuberculosis Hospital, and the Pulmonary Laboratory, Children's Hospital.

TREATMENT OF THROMBOPHLEBITIS WITH STREPTOKINASE-STREPTODORNASE

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and
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The buccal administration of streptokinase-streptodornase was tried in the treatment of a test group of 52 patients who had superficial thrombophlebitis as a complication after venoclysis. A contratest group of 22 patients, who received general treatment but neither the drugs nor a placebo, were observed for comparison. The investigator who evaluated the progress of the two groups did not know, in most instances, to which group a given patient belonged. The streptokinase-streptodornase was given either as one tablet (10,000 units) four times daily or two tablets every four hours; the tablet was kept in the patient's mouth until dissolved. Under these conditions no significant difference between the two groups was found, and no evidence of therapeutic or prophylactic action was obtained.

Streptokinase-streptodornase has been established for the past several years as an effective agent for topical use in liquefying purulent and fibrinous exudates. More recently it has been given intramuscularly for the treatment of hematoma, traumatic inflammation, cellulitis, abscess, and thrombophlebitis.[1]

Our present understanding of the effectiveness of streptokinase as a fibrinolytic and anti-inflammatory agent is that streptokinase reacts, by one or more reactions, with human serum to produce an "activator" substance which, in turn, reacts with serum plasminogen to produce the active proteolytic enzyme, plasmin. Plasmin lyses fibrin by converting it into many smaller polypeptide groups.[2] In common with other proteolytic enzymes, plasmin has been shown to have some anti-inflammatory effect.

Buccal administration of streptokinase-streptodornase (Buccal Varidase) has been developed because of fever, local pain, and other side-effects associated with the intramuscular preparation. The newer buccal preparation has been used to treat a number of inflammatory states, including thrombophlebitis.[3] Initial reports on the buccal use of streptokinase-streptodornase in the treatment of thrombophlebitis have been encouraging, as might be anticipated from our present understanding of the mode of action of streptokinase and reports that the drug is absorbed buccally. Because the number of cases reported has been small, however, and because to date no controlled studies have been reported, the present work was undertaken to test further the effectiveness of buccally given streptokinase-streptodornase in the treatment of thrombophlebitis.

Materials and Methods

Superficial thrombophlebitis after intravenous administration of fluids in the arms was used as the clinical situation in which to evaluate the drug. This insured that treatment and control series of patients would represent comparable kind and extent of disease. It also provided a lesion that could be readily evaluated and measured.

Seventy-four staff and private patients, who had the onset of symptoms within 48 hours of the beginning of treatment and were alert and cooperative enough to hold the tablet in the mouth until it dissolved, were selected for buccal treatment with streptokinase-streptodornase. All subjects were observed and treated for five to seven days or until all symptoms and signs subsided, whichever occurred first.

Superficial thrombophlebitis was diagnosed by the presence of inflammatory signs and symptoms, such as redness, warmth, swelling, tenderness, and pain and by the presence of a distinct palpable cord in the involved vein. Unless both inflammation and a palpable thrombus were present on first observation, the patient was not included in this study. These same criteria were also followed daily to determine the natural course of the disease in the control subjects and the effect of a buccal dose of streptokinase-streptodornase in the treated patients.

A control group of patients was selected at random during the course of the study. These patients were not given a placebo, but the investigator performing daily evaluations of the treated and control subjects did not know, in most instances, which were treated and which were controls. Treated patients were given either one buccal tablet of streptokinase-streptodornase (10,000 units) four times daily or two tablets every four hours.

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ence, −6.5%, could be due in part to resistance of the system, leakage, inertia, and differences in the recording apparatuses. The concentration of carbon dioxide inhaled by the operator varied from 4.25% at the beginning of respiration to 0 at the end, and for the victim it varied from 0 to 4.45%, with a mean of 2.6%. The mean oxygen concentration inspired by the victim was 16.4%. Although this value is less than that found in room air, it must be remembered that the first 300 cc. of air as well as the operator's dead space is essentially room air and this is the portion that enters the victim's lungs first. The adequacy of this type of ventilation is further supported by the arterial blood gas levels.

Chemical Effects.—The results of the arterial blood gas analyses are presented in table 3. In all subjects there was evidence of adequate ventilation during the mouth-to-mask resuscitation, as manifested by a fall in the PCO_2, a rise in pH, a fall in the carbon dioxide content, and a rise in the PO_2, compared with the period of unassisted breathing.

Clinical Effects.—Two subjects developed acute respiratory distress while breathing without assistance. After mouth-to-mask ventilation was begun they obtained immediate relief and remained comfortable throughout this period. Both subjects were hyperventilated during the control period while receiving respiratory aid. Symptoms of acute distress occurred when the PCO_2 was within the normal accepted range, although in each subject there was an abrupt rise in PCO_2 of 15 mm. Hg. In the subject with moderate respiratory acidosis, symptoms of acute hyperventilation developed, manifested by vertigo, drowsiness, and lightheadedness, while he was ventilated by the mouth-to-mask method. He became asymptomatic when artificial respiration was discontinued. Symptoms were due to the abrupt fall in the PCO_2 from 50.9 to 36.2 mm. Hg.

Comment

Mouth-to-mask resuscitation, with use of a simple piece of equipment like the one in this study, is safe and efficient. In all of the subjects satisfactory ventilation and arterial blood gas composition were demonstrated. Mouth-to-mask resuscitation eliminates contact with the victim, thus minimizing the danger of infection. Significant hyperventilation by the operator is prevented by his rebreathing the small portion of expired air remaining in the resuscitator tubing. The concentration of oxygen entering the victim's lungs is adequate and that of carbon dioxide low. An adapter placed at the inhalation inlet permits resuscitation with 100% oxygen from a demand or continuous flow system when oxygen is available.

This form of resuscitation may be used not only for an apneic patient but also as a short-term assister in the ventilation of subjects in respiratory distress. Ventilatory support can be continued until more specific medical treatment or mechanical devices are available.

It must be remembered that an unobstructed airway must be established and maintained before any form of artificial respiration can be successfully used.

Summary

The mouth-to-mask technique is a safe, simple, and efficient method of administering artificial respiration both in resuscitating apneic subjects and in providing assistance to persons in respiratory distress. It is recommended for widespread use. This type of breathing is as efficient as the mouth-to-mouth technique and superior to it, in that it reduces operator apprehension, hypocapnia, and fatigue. Further, if the unit is equipped with a pressure relief valve serious overinflation of the victim's lungs is avoided.

This study was supported in part by an annual grant from the National Foundation.

The mouth-to-mask unit used in this study was designed by Henry W. Seeler, of the Aero Medical Laboratory, Wright Patterson Air Force Base, Ohio, and supplied for evaluative purposes by the manufacturer, Globe Industries, Dayton, Ohio.

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treat thrombophlebitis, has shown little or no value in ameliorating the inflammatory changes or altering the thrombus itself. There is also good evidence that this drug is of no value in the prophylaxis of thrombophlebitis.

Summary

In a group of 74 patients with superficial thrombophlebitis after intravenous administration of fluid, 52 were treated with varying dosages of streptokinase-streptodornase (Buccal Varidase) for five to seven days, while 22 were observed as controls for the same period. Treatment was started in each instance within 48 hours of the onset of symptoms.

No significant amelioration of inflammatory signs and symptoms or alteration of the palpable thrombus itself was evident in the patients treated with the drug when compared to the control series. The drug did not provide prophylaxis against superficial thrombophlebitis.

This study was supported by a grant-in-aid from Lederle Laboratories, Division of American Cyanamid Co., Pearl River, N. Y., which also supplied the streptokinase-streptodornase used in this study as Buccal Varidase.

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ELECTROLYTE-FREE LIQUID FORMULA DIET

METABOLIC EFFECTS AND POSSIBLE CLINICAL USES

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Twenty college students, 19 men and 1 woman, subsisted for three to five days on a liquid diet containing 300 Gm. of carbohydrate, 100 Gm. of vegetable fat, and no protein. The unique feature of the diet was its almost complete avoidance of electrolytes; the elements ingested daily amounted to 45 mg. of sodium, 32 mg. of potassium, 2.7 mg. of calcium, 64 mg. of chloride, and 84 mg. of phosphorus. Daily 24-hour urine specimens were obtained from the students for two days of unrestricted diet and during the study period. Serum electrolyte and nonprotein nitrogen measurements were made during the prediet period and at the end of the diet period. The diet produced a prompt decrease in urinary electrolyte excretion. It was palatable and well tolerated. It promises to be useful in the diagnosis as well as in the treatment of various conditions in which electrolyte control is important.

The use of liquid formula diets has been well documented in medical literature. Ahrens and colleagues[1] maintained patients on liquid formulas for periods ranging from 2 to 16 weeks. Most of the formulas have been designed to provide maximum calories, vitamins, and minerals to patients or to attain weight reduction.[2] However, the presence of a high content of certain minerals or of protein is distinctly undesirable in certain clinical states such as chronic renal disease, congestive heart failure, chronic liver disease, and hypertension.

Electrolyte depletion in critically ill patients can be corrected by intravenously given fluids, and harmful electrolyte accumulations may be reduced with use of the artificial kidney, peritoneal dialysis, or diuretics. If diets free of electrolytes could be given in less critical situations, or as adjunctive therapy in the more severe cases, much greater control could be assured.

The difficulty with the dietary approach, up to this time, has been the almost complete impossibility of formulating a diet that is even reasonably low in mineral content. A special electrolyte-free

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Results.—The control group consisted of 22 patients. The bar graph (fig. 1) shows that the inflammatory symptoms and signs of superficial thrombophlebitis persisted from two to seven days, with a mean duration of symptoms of four and eight-tenths days. With the exception of two subjects in whom the palpable thrombus disappeared on the fifth day, a palpable thrombus was present in every subject on the seventh day, the end of the observation period.

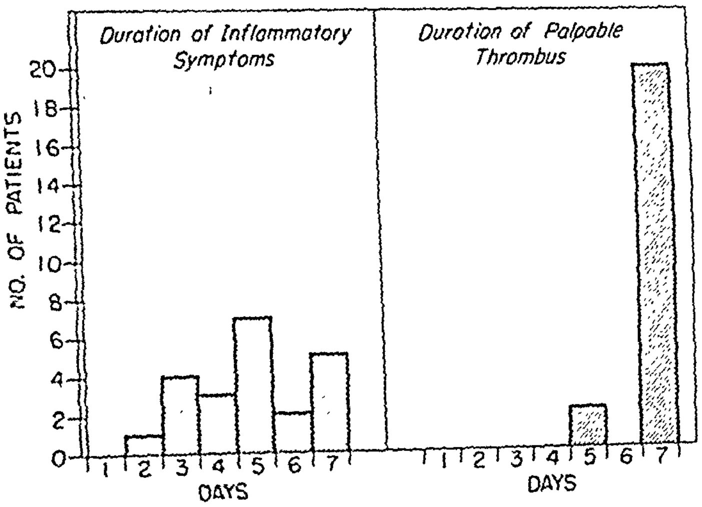

Fig. 1—Control series of patients with thrombophlebitis: no treatment with streptokinase-streptodornase; mean duration of symptom 4.8 days.

The first treatment group consisted of 17 patients treated with one buccal tablet of streptokinase-streptodornase four times daily. In these patients inflammatory signs and symptoms lasted three to seven days or longer, with a mean duration of five and six-tenths days. A palpable thrombus was present on the seventh day in all but one patient, in whom it disappeared on the fourth day (fig. 2). Thus, this treatment group showed no significant difference in any respect from the control group.

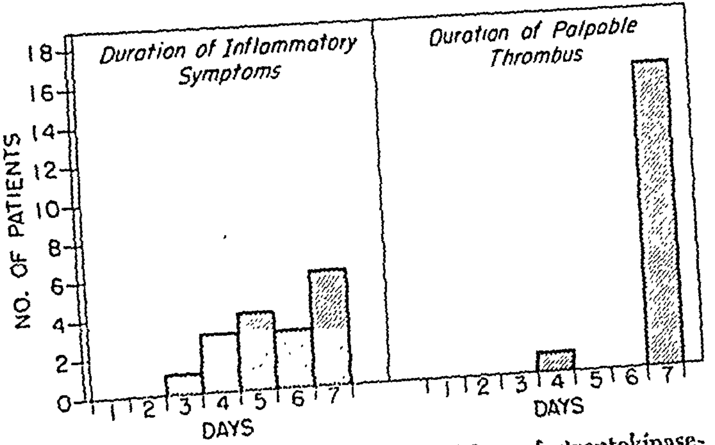

Fig. 2—Treatment group 1: four tablets of streptokinase-streptodornase daily; mean duration of symptoms 5.6 days.

A second treatment group consisted of 35 patients treated with two buccal tablets of streptokinase-streptodornase every four hours, a total of 12 tablets daily. In this group inflammatory changes persisted two to seven days or longer, with a mean duration of four and two-tenths days. The palpable thrombus noted on the first day of observation was unchanged at the conclusion of the study in all but two patients, in whom it disappeared on the third and fourth days, respectively, after onset of symptoms (fig. 3). The mean difference in duration of inflammatory symptoms and signs in this group compared to the control group was considered insignificant in a series of this limited size. The persistence of the palpable thrombus was almost identical in the two groups.

Other findings in the course of the study shed light on the value of buccally given streptokinase-streptodornase for the prophylaxis of thrombophlebitis. Five patients in the group treated with the drug developed fresh phlebitic processes in the opposite arm or in the leg while receiving treatment for their original phlebitis. These subsequent sites of thrombophlebitis showed inflammatory changes similar to the original lesions in duration and intensity. One patient who was being treated for a superficial phlebitis of the left forearm developed deep thrombophlebitis of both legs on the sixth day of therapy and several days later had a pulmonary embolus. In four other patients the phlebitic process, under observation, showed a progression of symptoms and extension of the palpable thrombus after treatment had been in progress for two days or longer.

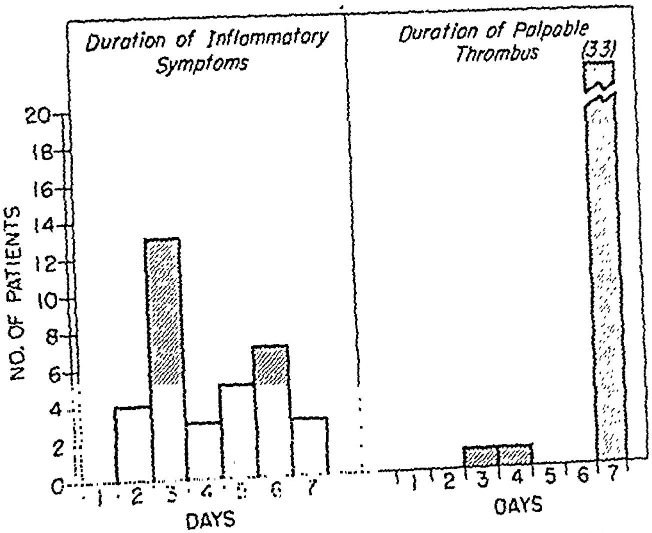

Fig. 3—Treatment group 2: 12 tablets of streptokinase-streptodornase daily; mean duration of symptoms 4.2 days.

In none of the treated patients was there any evidence of fever, vomiting, or other side-effects that could be attributed to the drug, with the exception of one patient who was nauseated after swallowing the medicament rather than retaining it buccally.

Comment

In view of the above results in a series of patients that was controlled and standardized within the limits of clinical feasibility, it must be concluded that, while streptokinase-streptodornase administered locally and topically has proved a valuable therapeutic tool, its buccal variant, when used to protein catabolism probably took place. Urinary nitrogen studies will be done to verify this. Preliminary data indicate that such a loss does not occur in hospitalized patients.

The NPN and serum electrolyte values before and at the conclusion of the study period are shown in the table. There are variations toward both an increase and decrease in values but all are within the normal range and no significant change is apparent.

Fifteen of the students had a decrease in urine volume to less than 700 cc., with an increase in specific gravity. The other five had urine volumes greater than 1,000 cc., with a correspondingly lower urine specific gravity. The latter group ingested increased amounts of fluid during the study period.

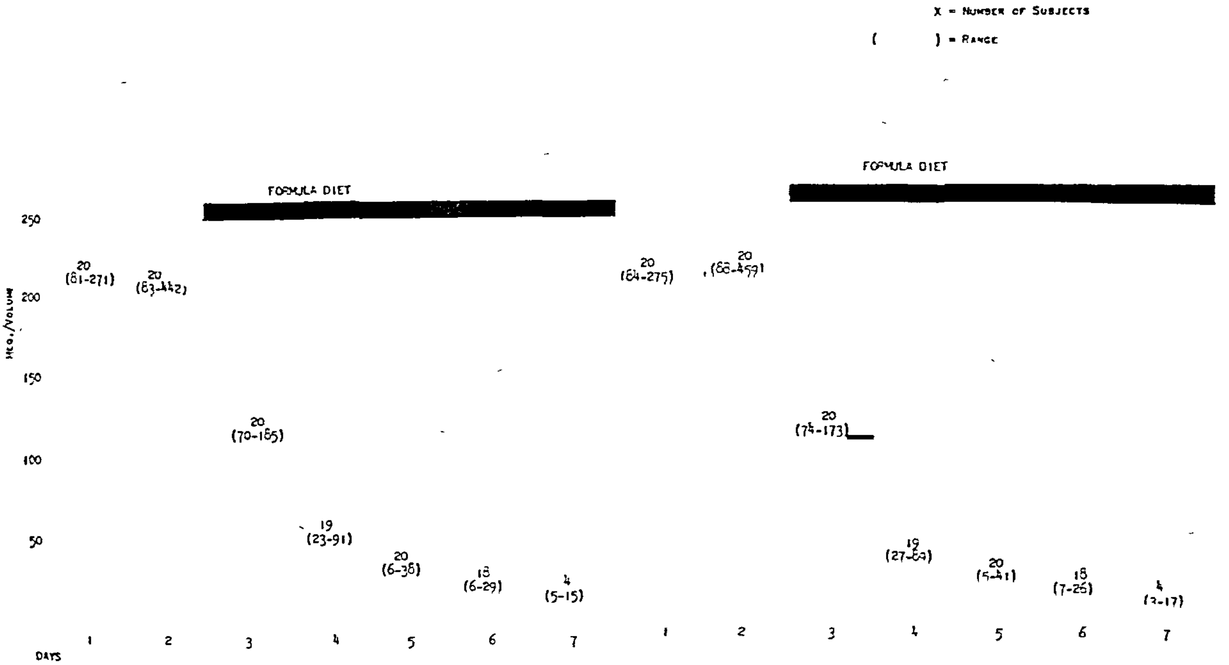

Fig. 1.—Parallel excretion of sodium and chloride; *left,* average urinary sodium output; *right,* average urinary chloride excretion. Note decrease in excretion of electrolytes.

In figures 1 to 4 are demonstrated the daily average 24-hour urinary excretion of electrolytes. The range, as well as the number of subjects on each day, is included. Days one and two are base-line days, with the subjects on an unrestricted diet, while days three to seven, inclusive, are with the subjects taking the formula. Figure 1 shows the parallel excretion of sodium and chloride. There is a stepwise decrease in excretion of these electrolytes and by the third day of taking the formula, minimal urinary levels are approached. Figure 2 shows the degree of potassium excretion in the urine, and it can be seen that there is a plateau of values after the second day on the formula. Figure 3 demonstrates the stepwise drop in urinary calcium excretion; while Figure 4 illustrates the gradual drop in urinary phosphate excretion.

Thus, a consistent, predictable, and rapid decrease in urinary electrolyte excretion has been demonstrated when normal subjects receive a moderate caloric intake essentially free of all electrolytes.

Comment

The need for a liquid formula diet containing virtually no electrolytes is apparent. Therapeutically, patients with edema due to cirrhosis of the liver, congestive heart failure, nephrosis, and other edematous disorders in which sodium retention is a factor, may be benefited. Severe sodium restriction could help mobilize edema fluid in patients with massive anasarca or refractory edema. Patients who cannot adhere to routine low-salt diets might be benefited by periodic use of the formula as an adjunct to other therapies. Finally, cachectic patients with edema can be given a substantial number of calories, either orally or through a gastric tube, without increasing their sodium intake. Patients with both acute and chronic kidney disease can be aided by such a diet. High-calorie diets with a minimum of fluid and no protein or harmful electrolytes, such as potassium, can be given during the oliguric phase to patients with acute renal failure. In patients with chronic renal disease, acute exacerbations with uremia might be helped by such a formula. Electrolytes as well as protein could be added to the formula as needed in various diseases. The diet also could be used as a food supplement during the course of chronic kidney disease with uremia.

liquid formula diet has now been made available which fills this requirement. In addition, the diet is devoid of protein so that the intake of this food element too may be avoided or controlled when necessary. As an additional possibility, the electrolyte-free diet could provide the sole dietary intake for clinical or metabolic balance studies in which intake must be constant and defined.[3]

In this paper the effect of an electrolyte-free diet on urinary electrolyte excretion and blood chemistry values when given to normal subjects will be described. In addition, the possible application of such a diet to clinical problems will be discussed.

Method

Twenty normal college students, 19 men and 1 woman, volunteered to be subjects for the experiment. They were given the liquid diet for three to five days. This was supplied as a liquid concentrate (Controlyte) containing 300 Gm. of carbohydrate, 100 Gm. of vegetable fat, and no protein. The carbohydrate consisted of equal quantities of simple sugars (maltose and dextrose) and higher levels of polysaccharides. The unique feature of the diet was the almost complete avoidance of electrolytes. Thus, the total daily intake of 400 Gm. of liquid concentrate formula contained only 45 mg. of sodium, 32 mg. of potassium, 2.7 mg. of calcium, 64 mg. of chloride, and 84 mg. of phosphorus. This represents a 98 to 99% electrolyte removal as compared to a normal diet.

The subjects were instructed to dilute the formula with two parts of water so that the 2,100 calories would be supplied in a total volume of about 1,100 cc. They were allowed to drink all the water, black coffee, or tea they desired and were allowed to chew gum. Daily 24-hour urine specimens were obtained for two days while the students were on an unrestricted diet and throughout the study period. The serum electrolyte and the nonprotein nitrogen (NPN) levels were measured during the prediet period and at the conclusion of the last day on the formula diet. Daily weights were recorded and blood pressures were obtained before and at the conclusion of the experiment.

Results

Although the formula was a marked deviation from the students' usual food intake, it was well tolerated. This was ascertained by daily personal interviews conducted by three different interviewers. The most common complaints were related to a sensation of fulness and a sweet taste after ingestion of the formula. Four of the subjects mentioned that their stools were softer than when on a normal diet. However, these were well formed and no diarrhea was reported. Hunger was not a complaint of the group and most of them went about their usual work, including physical exertion, without any difficulty. Six of the subjects had a craving for solid food while on the study. There was no significant change in blood pressure during the study.

Weight losses ranging from 3 to 11 lb. (1.3 to 5.0 kg.), with an average of 5.75 lb. (2.64 kg.), occurred during the study period. The 2,100 calories per day provided by the formula were inadequate for such active subjects and some weight loss was anticipated. This decreased caloric intake, however, cannot account for the degree of weight loss documented. The urine volumes indicated that fluid loss also did not produce the fall in weight, since most of the urine volumes decreased. Therefore, changes in body composition probably accounted for the loss. The diet contains no protein, and endogenous

Serum, Nonprotein Nitrogen (NPN), and Electrolyte Values in Excreted Urine Before and After Liquid Formula Diet

NPN, Mg. %		Sodium, mEq/L.		Potassium, mEq/L.		Chloride, mEq/L.		Calcium, Mg. %		Phosphorus, Mg. %	
Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
35	32	149	151	4.8	4.2	107	106	9.5	9.2	3.4	3.8
34	33	143	147	5.5	5.6	106	105	9.7	9.5	3.3	3.5
33	38	144	149	4.8	5.1	111	110	10.0	9.4	4.0	3.6
32	37	143	150	5.7	4.6	103	103	9.4	9.8	3.3	3.8
33	37	145	148	5.8	5.2	107	106	10.9	9.4	3.1	3.5
33	35	150	147	5.5	5.7	109	108	9.0	9.3	4.0	4.3
33	33	143	153	5.2	5.8	102	111	9.1	9.7	3.9	3.6
31	35	146	150	5.5	5.2	107	107	9.4	9.7	3.6	3.6
30	32	149	151	5.8	5.2	108	114	9.4	9.3	3.8	3.8
41	36	147	146	5.2	4.6	108	99	9.6	9.5	3.5	3.9
36	28	147	146	5.8	5.8	110	106	9.1	9.1	3.4	3.7
38	33	152	146	5.2	5.3	105	109	9.7	9.6	3.5	3.5
35	31	147	151	5.7	5.3	109	106	9.3	9.3	4.1	4.1
31	33	145	152	4.9	5.0	110	105	10.1	9.0	4.7	4.3
28	29	147	153	5.3	4.9	111	104	9.4	9.6	3.1	3.3
31	33	148	147	4.5	4.9	102	111	9.7	9.7	3.5	3.4
35	32	146	148	5.6	5.8	103	107	9.9	9.6	3.3	3.5
37	31	149	142	5.1	4.2	111	104	9.4	9.0	4.0	4.0
35	34	149	153	5.6	5.5	107	107	9.9	9.5	3.7	3.7
42	42	144	137	4.6	3.5	106	106	9.3	9.1	3.6	3.3

The liquid diet concentrate used in this study was supplied as Controlyte by Norval G. Barker, Ph.D., of the Dietene Company, Minneapolis.

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FUNCTIONAL RESTORATION OF THE PATIENT AT HOME

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and
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Convalescent patients discharged from a hospital do not always solve all of the problems of adjusting to the home situation. The advantages of a home program are evident, but an effort must me made to keep the patient from slipping back into his former role of dependency. The classification of disabilities given here can serve as a guide to the home needs of the patient. Numerous assistive devices are available, but patients sometimes need to be informed about them and to be encouraged to use them. The family may need instruction about such devices and about orthopedic appliances, special clothing, and modifications of the home for specific handicaps. The physician, by judicious consultation with others in medical specialties and paramedical fields, can do much to increase the patient's self-sufficiency and to improve patient-family integration.

Aiding the patient to achieve the highest degree of self-sufficiency is the ultimate goal of any medical program. In working toward this goal, the physician responsible for the over-all medical management may incorporate many of the methods and techniques of physical medicine and rehabilitation. These therapeutic procedures are of particular value in the functional restoration of the chronically ill and the disabled patient at home.

Reasons for Program in the Home

For the patient who can afford the services of a private rehabilitation center or who has a county center available to him, the need for additional treatment and training at home may not be too apparent. However, the functional activities learned in the supervised hospital situation are not always carried over into the home environment. Often this is because the furniture, stairs, and utilities at home do not match exactly the equipment at the center where the patient learned the techniques of self-care and functional independence. Also, the transition from a hospital ward with other patients having similar disabilities and problems to a home situation where he is the only disabled person may cause emotional conflicts. This can seriously inhibit his improvement or interfere with the maintenance of his functional level.

Sometimes, the family is unable to solve the many problems which arise when a disabled member must adjust to a home situation. Frequently the family hesitates to question the professional staff at the center regarding the role of the family in guiding the patient toward independence. Therefore, unless there is additional retraining in the home, the patient may find it easy gradually to slip back to his former role of dependency.

The advantages of a home program for disabled or long-term convalescent patients discharged from a general hospital are evident. Because of the high costs and the limited facilities for rehabilitation in the hospital, the patient rarely remains after the acute phase of his illness has passed. In many cases, this may be long enough for him to have grown accustomed to the total care he received during his stay. After his discharge, the family may try to

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From the May T. Morrison Center for Rehabilitation and the State Department of Social Welfare (Dr. Montero); Director, Home Care Rehabilitation (Miss Rosenberg).

Patients with hypertension can also be aided by use of such a formula. Those with malignant hypertension, in which all methods available for pressure reduction should be used, can temporarily be placed on the diet. The chlorothiazide group of drugs are effective in part in lowering blood pressure by their natruretic effect. *It is possible that* initially "priming" patients with essential hypertension with the diet and then administering one of the chlorothiazide drugs, or administering the drug along with the diet, might control the patient's hypertension more rapidly and smoothly.

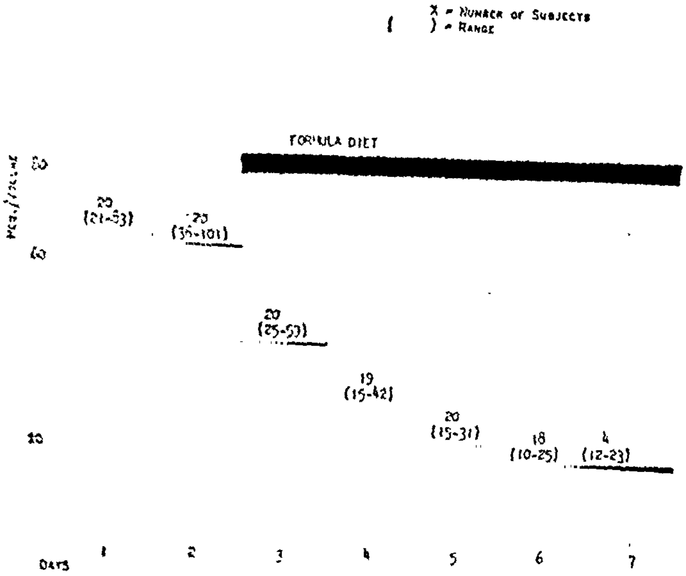

Fig. 2.—Potassium excreted in urine (average). Note plateau of values after second day on formula.

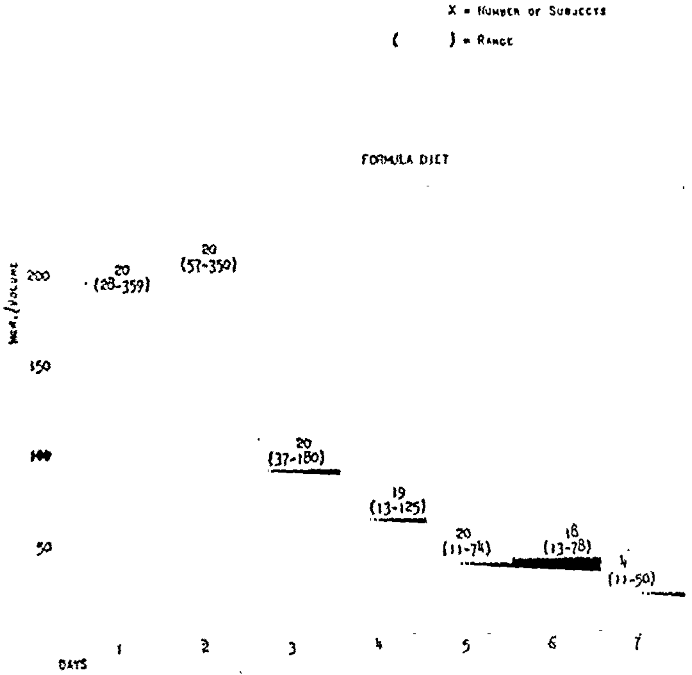

Fig. 3.—Average urinary calcium excretion. *Corresponding drop in urinary calcium levels, with use of formula, is demonstrated.*

The diagnostic uses of a nonelectrolyte liquid diet are multiple. In metabolic studies special diet kitchens, trained personnel, and multiple laboratory determinations are required to estimate the intake. Since this entire procedure can be eliminated, if the formula is the patient's sole dietary intake, clinical metabolic studies can be routinely done in any fair-sized hospital. Sodium metabolism in edematous states and calcium metabolism in the study of patients with renal calculi, hyperparathyroidism, malignancies, and sarcoidosis are a few examples of the possible diagnostic uses. This type of diet, therefore, would appear to be of value for many conditions in which ingestion of electrolytes or protein must be avoided or controlled.

A limiting factor in the use of such formulas is, of course, their palatability. The study on the 20 subjects showed that, even though these persons did not have the stimulus of a disease to encourage them to continue taking the formula, acceptance was exceedingly good. This is in contrast to many previous studies with formula diets containing a high ratio of fat calories in which intolerance occurred frequently. The metabolic studies demonstrated the rapidity of urinary electrolyte changes that can be achieved on such a diet. I will continue the use of this formula in an attempt to ascertain its usefulness in the above mentioned areas.

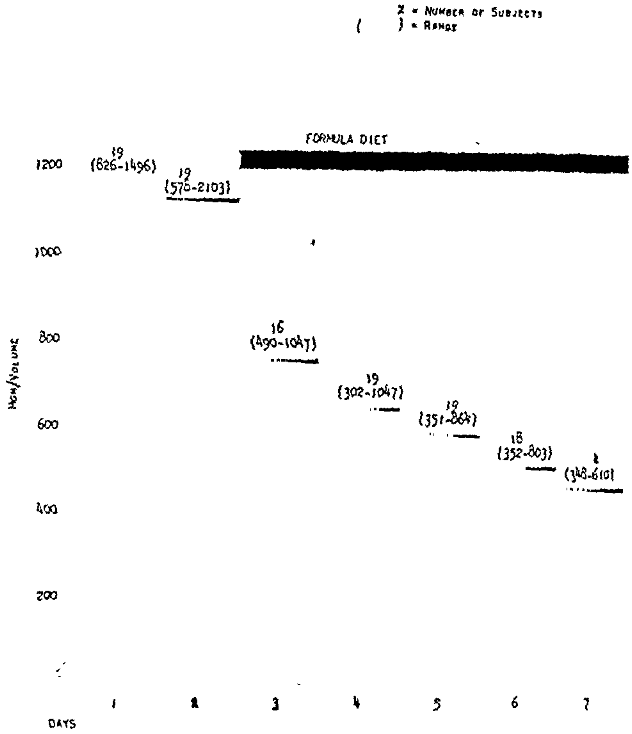

Fig. 4.—Average urinary excretion of phosphorous. There is gradual decrease during use of formula.

Summary

Twenty normal subjects were placed on a specially prepared liquid formula diet free of electrolyte and protein content. A rapid and predictable decrease in urinary electrolyte excretion was demonstrated. The diet was palatable and well tolerated by the subjects. There are many possible clinical applications of such a formula.

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ciency, and (3) to permit reduction in attendant care. In general, indications for modifying the home will be influenced by the degree and type of functional impairment of the patient.

Group with Limitations of the Lower Extremity.—If the impairment affects ambulation or control of the lower extremity, as in rheumatic diseases, amputations, and neuromuscular disorders, changes in the home may include hand rails where steps are unavoidable, removable ramps, nonskid finishes on floors, and strategically placed grab bars. The furniture might be arranged so that the patient can maneuver around the room with ease and use the furniture for support if necessary. In certain cases a raised toilet seat, a stool in the shower, or a bench in the tub might make toilet activities easier. The standard type door to some rooms might be replaced by curtains, accordion doors, or sliding doors, and it might be necessary to remove part of the doorway molding for added space. An overhead trapeze on the bed, side rails, or special bed frame might be used to eliminate the need for assistance in getting in and out of bed. The patient might benefit from shelves, cabinets, and closet bars at a lower level than usual if he is confined to a wheel chair for most of his waking hours. Tables and desks, on the other hand, should be somewhat higher in order to accommodate the wheel chair.

The patient affected with rheumatoid spondylitis, whose spine and hips are ankylosed in the extended position, presents a completely different problem. Most activities must be performed while standing up or lying down. This patient could probably perform better if the furniture, bed, cabinets, tables, toilet, and desk were at a higher level than normal.

Group with Limitations of the Upper Extremity.—Patients whose problems involve mainly the use of the arms will benefit from some changes in the home. If the impairment is mostly due to loss of range of motion, as may occur in certain bone or joint diseases, the modifications to the home might be geared to bringing all necessary equipment and furnishings within the patient's optimal functional range.

If incoordination of the upper extremities exists, as in some types of cerebral palsy, multiple sclerosis, or hereditary ataxia, concern should be with sturdy furniture, weighted utensils, and enlarged knobs, handles, switches, and drawer pulls. For those patients who have uncontrolled exaggerated motions, particular attention should be paid to the safety factor in the home. Furniture with sharp or protruding parts, fragile or dangling objects, and highly inflammable materials should be eliminated or kept at a minimum.

When weakness and paralysis are the deterrents to functions of the upper extremities, as seen in patients with poliomyelitis and certain types of traumatic or toxic neuritis, the weight and size of movable objects should be compatible with the patient's strength. The height and depth of closets, cabinets, stove, and sink should be evaluated as to accessibility and modified accordingly. Light-weight furniture and utensils which can be rolled or slid, rather than lifted, may make keeping house easier.

Group Requiring Total Care.—More and more patients requiring total care are living at home rather than in nursing homes or hospitals. In many cases a member of the family is completely responsible for this care. Some patients may require full or part time nursing care. The patient with quadriplegic poliomyelitis, the decompensated cardiac, and the bedridden geriatric patient are among the many belonging to this group.

Modifications in the home of this type of patient should be aimed at making the assistance that the patient requires more effective and increasing his active participation in the family group. Bed care will often be easier if a hospital bed is used. An overhead trapeze, side rails for the bed, and an adjustable bedside table may also help.

Lifting or moving the patient can usually be accomplished by one attendant if a hydraulic lift is used. When possible, the patient's room should adjoin the bathroom and be large enough to accommodate all of his equipment. If the bathroom is not accessible, a chair commode might be used as a substitute.

It is important to keep in mind, however, that much of this equipment is large and bulky as well as costly. Careful measurements of the areas where the equipment will be used and weighing of the relative benefits against family income should be done prior to recommending any new purchases.

The room should be well ventilated, uncluttered, and cheery for the patient's benefit and to encourage visitors. If possible the telephone should be within reach of the patient, and bedside radio, books, magazines, and assistive devices should be close by.

It should be apparent that the more-or-less arbitrary breakdown of disease and disability groups listed here will give the physician only a tentative guide to the home needs of a specific patient. Persons with similar disabilities will often exhibit completely different functional levels which may be due to differences in motivation, intellect, previous training and treatment, personality, and socioeconomic factors.

Assistive Devices, Orthopedic Appliances, and Clothing

Assistive Devices.—Mechanical aids to assist the patient in his achievement of independent living have been developed by rehabilitation personnel in hospitals and rehabilitation centers. Ingenious patients have devised numerous gadgets to help solve some of their particular problems. Publications listing and describing many of these aids can be found in the libraries of most large hospitals or medical duplicate that care, and then, instead of making continued progress towards recovery with the gradual withdrawal of help, some patients become more dependent and demanding. Often deterioration, both physical and mental, may occur which has no relation to the original disability.

There are many chronically ill persons who were not hospitalized during any phase of their illness. Many of these people are being treated by their family physician. He sees them at more or less regular intervals to prescribe some type of maintenance medicament and occasionally fills out an insurance form. Here, neither the patient nor his family expects to see any noticeable improvement in the medical or functional picture.

Sources of Professional Assistance

It should be obvious that, in the groups mentioned, there will be many persons who have the potential for greater self-sufficiency. To exploit this potential to its fullest, the physician should be familiar with those rehabilitation services in his community which are set up to make home visits. In some areas medical consultation with a physiatrist could be sought before a goal is set up or a program planned. Visiting physical and occupational therapists may be available through private facilities or community chest organizations. Home nursing services are often rehabilitation oriented and may be able to assist the physician in carrying out a functional improvement program.

Evaluation of the Patient

In planning a practical rehabilitation program for the patient, it will be necessary to evaluate his abilities as they relate to his home environment. This requires, first of all, an accurate medical diagnosis as well as a prognosis, including any limitations and precautions.

Determination of Functional Level.—The functional level of the patient should be ascertained by testing his ability to perform the activities of daily living. To be of practical value these tests should be given in the patient's home. His ability to dress and undress himself, to get in and out of bed, to feed himself, to use toilet facilities, and to maneuver in and around his home should be among the tests given. The activities should be graded as to ease, safety, and speed of accomplishment. The amount of assistance necessary should also be noted. Assistance might be in the form of mechanical aids such as prosthetic devices or actual manual help of another person in the home. Since the activities of daily living may differ greatly between a housewife, who must care for a large family, and an elderly person living alone, the tests should be planned to cover those areas which will give the most insight into the specific functional problems of the patient.

Home Evaluation

With the functional level established, it becomes necessary to evaluate home structure and furnishings. It should be determined what the limiting factors are and what changes may be required in order to increase the patient's level of self-sufficiency.

Ideal Home.—Ideally, a home for a disabled person would be equipped with all the labor-saving devices and electronic gadgets that modern technology can offer. It is now possible to build a house with floor space, cupboards, doors, bathroom, and kitchen designed so that a handicapped person can accomplish many more activities than he would be able to achieve in a standard house. Of course, requirements will vary with the extent and type of disability as well as with the functional status of the patient. For example, a paraplegic patient, who is confined to a wheel chair and who has normal use of his upper extremities, could perform better in a home that had been planned with all the rooms at ground level. The garage might have a remote-control door. A built-in lift might be used to help the patient in and out of the car. The rooms in the house could have extra wide entrances without door sills and could be larger than normal for easy maneuvering of a wheel chair. A bathroom could be designed so that the tub and toilet are at wheel chair level; the wash basin high enough for the wheel chair to roll under, and the stall shower flush with the floor. A kitchen with a built-in oven at wheel chair height, low refrigerator and cabinets, pull-out or revolving shelves, pass-through counters, and a sink which can be easily reached may make meal planning and preparation possible.

Standard Home.—Unfortunately most handicapped people must live in homes designed for normal persons. Usually these are rented houses or apartments where structural changes are rarely permitted or are too costly for consideration. Even when the home is owned by the patient, many people hesitate to make permanent changes which may jeopardize the resale value. Therefore, it is necessary to evaluate the existing home and facilities to estimate the temporary changes which may be needed. This evaluation should also give information as to the most economical and practical use of an attendant when necessary. At the same time, the need for self-help devices, functional training, and retraining will become apparent.

Home Modification

Any recommended changes or modifications in the home should be carefully considered by the physician and discussed with the patient and his family. To be effective these changes should be aimed at one or more of the following goals: (1) to allow the patient to accomplish additional functional activities, (2) to increase the patient's effi-

and are often amateurish in appearance. Great care should be taken in recommending appliances of this sort as they can rarely be had on approval and often take so long to be manufactured that the patient may lose interest in accomplishing the activity before he receives the appliance.

Role of Exercise

It is now generally accepted that even for the most severely handicapped persons a certain amount of physical activity can be beneficial. Maintenance of range of motion, prevention of decalcification of immobilization, improvement of venous and lymphatic circulation, and prevention of disuse atrophy are some of the general beneficial effects of exercise. However, an effective exercise program for the patient must be based on his functional needs, rather than on the function of specific joints or muscles. The aim of an exercise program is not to bring the muscle power, coordination, range, and endurance to normal limits but to bring about the greatest degree of functional independence. Helping the patient to organize his day so that his training and exercise program is an integral part of his daily schedule will help build good habits and make sure that the prescribed treatment program is carried out. In most cases it is not necessary to purchase expensive gymnastic equipment as, since the functional restoration should be geared toward independence in the home, the patient will use the existing home facilities whenever possible. In certain cases sandbags, pulleys, mats, parallel bars, or other equipment may be purchased or improvised.

Comment

The ever increasing population of chronically ill and disabled patients living at home presents serious medical and socioeconomic problems. The family physician can attack many of the medical problems if he is willing personally to direct a dynamic treatment program geared toward functional improvement. By the judicious use of the consultative services in the medical specialties and paramedical fields he should be able to set up a specific and practical therapeutic plan. Improved self-sufficiency, better patient-family integration, and prevention of deterioration and stagnation are a few of the results and rewards of this kind of program.

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THE NEWBORN INFANT AND SURGERY.—Newborn infants have instability of temperature regulation, respiratory and cardiac reserve, low concentration of plasma protein, and transient hypothrombinemia. . . . Because the neonate possesses a small amount of subcutaneous fat and a large body surface, heat loss is more rapid than in the child or in the adult. To be prepared for operation the body temperature of the neonate should be approximately normal. This can be achieved by having the infant in an incubator. . . . The incubator also can provide a concentration of oxygen under absolute control. The newborn infant awaiting surgery for correction of tracheo-esophageal fistula, diaphragmatic hernia, or intestinal obstruction with distention is greatly improved by administration of adequate amounts of oxygen. . . . The body temperature of a full-term newborn at the close of a major operative procedure may be 90 to 95 F. This degree of hypothermia does not have any untoward effect on the recovery of the patient—it may even be of benefit. Metabolic processes are slowed and the infant is protected to some extent from possible effects of anoxia . . . The normal infant's body composition is 77% water and 23% solids, in contrast to 60% water and 40% solids for the normal adult. The infant experiences a physiological dehydration for three to four days after birth. Operation and starvation increase the weight loss. Losses of 10 to 15% of body weight are tolerated quite well. . . . Preoperative parenteral fluid [administration] may be totally unnecessary or even contraindicated. . . . The newborn infant undergoing a surgical operation should be on the "dry side" as far as parenteral fluids are concerned. If the infant requires prolonged intravenous alimentation, protein can be administered as serum albumin, human plasma, or protein hydrolysates. . . . Recognition of the specific differences in the physiological mechanisms exhibited is essential to the attainment of satisfactory results in the surgical treatment of newborn infants. Successful management requires close supervision of electrolyte balance and blood volume, an adequate oxygen concentration in the environment, maintenance of body temperature, and careful selection of the diet as well as the prevention of cross-infection.—C. D. Benson, M. D., and E. E. Martmer, M. D., Preoperative and Postoperative Care of the Newborn, *The Surgical Clinics of North America,* December, 1959.

schools. Many hospital supply house catalogues now include a list of rehabilitation equipment and self-care devices. While some are products of scientific research, such as special hand controls for the operation of an automobile by a paraplegic, others are crude but effective improvisations. Prices vary from pennies to thousands of dollars, depending on the complexity of the devices as well as production costs.

Orthopedic Appliances.—Braces, crutches, wheel chairs, prostheses, and splints may be necessary to aid the patient to improve his functional level. A carefully individualized prescription, adequate training in the use of the appliance, and a well-motivated patient may make the difference between success and failure of a functional improvement program.

Clothing.—The difference between a "sick" person living at home and a disabled family member can often be seen in the simple fact that the former is unkempt, unshaven, and usually wearing an old flannel robe, whereas the latter is fully clothed and well groomed. The psychological effects of a careful toilet and clean, neat clothing can do much to improve the morale of the patient, his family, and his visitors. Proper clothing should be comfortable, attractive, and easily put on and removed. The fabric should be able to withstand the pressure and friction of appliances. Highly inflammable fabrics should be avoided, and weight as well as warmth of the material should be evaluated. Unusual dryness of the skin; abnormal perspiration; and presence of sensory, trophic, and circulatory disturbances should be taken into account when a wardrobe is planned.

It is not always necessary to purchase an entire new wardrobe in order to simplify dressing activities. Much of the clothing that the patient has can be remodeled or adapted to conform to his limitations. Long zippers down the sides of trouser legs can be of great advantage to a person wearing leg braces. Snaps instead of buttons, moccasin-type shoes or elastic shoelaces, wrap-around skirts, and pretied neckties are a few of the changes which can be introduced.

Indications for Use.—When one considers the prescription of a self-help device, orthopedic appliance, or special clothing, it is not enough to believe that they will be of value simply because they were designed to assist a patient in accomplishing a specific task. It is not unusual to visit the home of a severely incapacitated person and find a solicitous family member spoon-feeding him, though a careful search of the home will reveal dust-covered devices specially designed for self-feeding. If the search is continued unused corrective braces, a hydraulic lift, ingeniously designed splints, and other mechanical aids may also come to light. This does not necessarily mean that most patients will refuse to use the devices which have been prescribed; however, the prescription should be preceded by a detailed investigation of the practicability of the device and the patient's motivation toward its use. The following questions should be answered. 1. What functional activity will be improved? 2. Will this device limit any necessary functions? 3. Can it be used with ease in the patient's home? 4. Is the cost within the patient's means? 5. Are repair and replacement parts easily available? 6. Does the patient want to accomplish the activity enough to invest the time, energy, and money required to become proficient in its use?

Work-Simplification and Work-Saving Devices

Time and motion studies of the so-called normal person during work and play have produced some amazing facts. Habit, fashion, and mores are often more important than efficiency in the performance of everyday tasks. The healthy body has a large reserve of neuromuscular energy which can be wasted without any apparent discomfort. Therefore, it is important to analyze the activities which the patient may need to perform and eliminate all but the essential motions required. For example, a patient discharged from a hospital after suffering a disabling illness may find himself unable to perform many of the physical activities required for the accomplishment of daily living simply because he is attempting to perform them exactly as he did prior to the disability.

Waste motion and duplication of work, which occurs because of insufficient planning, should be eliminated whenever possible. A housewife could save time and energy by doing most of her shopping by phone or mail when going to the store is difficult. She should plan her day so that the hardest work is done when her energy is at its highest level. Frequent short rest periods are often more beneficial than one long one. Organizing the space in the home so that all materials for one job are in one area can save many steps. A tea wagon with large wheels can make setting and clearing the table possible for someone who has difficulty in carrying objects.

Today industry is turning out an infinite number of devices, appliances, and gadgets aimed at eliminating, or at least reducing, much of the drudgery involved in homemaking and work activities. Remote control lawn mowers, automatic washers and dryers, electric typewriters, electronically controlled door openers, tape recorders, room-to-room intercoms, push-button telephones, electric can openers, and wash and wear fabrics are only a few examples. The disabled person at home should, if economically possible, take advantage of as many of these devices as will benefit him. There are, of course, especially designed appliances for the handicapped person which will allow him to perform more efficiently as well as accomplish additional activities. Since, for the most part, these must be individually produced, they are expensive lated. Maps show soft water areas to comprise the Atlantic and Gulf Coast states, except for Florida, and the Pacific states. Areas inland vary in a more or less regional manner.[5] (Areas with states having water with hardness above the national average [97 parts per million] are east north central, west north central, and mountain states except New Mexico. Florida is the only south Atlantic state, Kentucky the only east south central state, and California the only Pacific state with water harder than the national average.)

Kobayashi,[6] in Japan, drew attention to the remarkable coincidence of high death rates from cerebral hemorrhage in areas where the river waters tended to be acid, i. e., where the sulfate-bicarbonate ratio was higher than 0.3. I analyzed his data

Table 1.—*Average Annual Age-Adjusted Total Death Rates from Cardiovascular Diseases (per 100,000 Persons), 1949-1951, and Weighted Average Hardness of Finished Municipal Water, 1950-1951, by State**

				Cardiovascular‡ Diseases			Coronary Heart Disease §	All Other Cardiovascular Disease
State	Hardness† (Ppm)	All Causes	All Causes Except Cardiovascular	Total	Male	Female	Male	Male
South Dakota	299	738.1	380.5	357.6	420.9	286.7	202.7	218.2
Nebraska	247	712.2	369.3	342.9	419.7	266.3	193.1	226.6
New Mexico	237	**871.5**	**581.3**	290.2	334.3	240.7	148.2	186.1
Indiana	237	828.0	402.5	**425.5**	**516.1**	338.7	242.7	**273.4**
Arizona	216	**906.8**	**572.3**	334.5	415.5	245.8	193.9	221.6
Iowa	212	717.0	351.1	365.9	447.3	287.7	228.1	219.2
Utah	191	754.7	385.8	368.9	450.4	289.3	222.9	227.5
Kansas	176	732.3	373.1	359.2	441.7	280.2	216.0	225.7
Wyoming	171	821.7	**448.4**	373.3	441.4	289.4	206.7	234.7
North Dakota	170	746.5	381.7	364.8	422.9	296.3	194.8	228.1
Wisconsin	167	771.2	366.2	405.0	475.5	334.2	242.3	233.2
Illinois	156	**874.7**	417.3	**457.4**	**549.1**	**369.3**	**255.5**	**293.6**
Ohio	150	828.0	408.4	419.6	504.8	338.8	**252.0**	252.8
Nevada	135	**970.5**	**547.2**	423.3	**514.7**	297.8	**268.0**	246.7
Texas	132	820.7	**463.0**	357.7	443.3	275.3	208.5	231.8
Oklahoma	125	742.4	407.8	334.6	418.1	252.1	193.5	224.6
Florida	123	842.5	**448.7**	393.8	484.6	306.5	229.7	254.9
Montana	120	843.6	**447.2**	396.4	468.2	308.4	220.2	248.0
Idaho	119	773.7	397.4	376.3	447.9	293.1	223.3	224.6
California	118	808.3	395.1	413.2	**516.8**	316.5	**295.6**	**221.2**
Michigan	115	842.0	420.3	421.7	500.1	341.1	**255.9**	244.2
Minnesota	114	729.0	354.0	375.0	448.8	299.6	230.0	218.8
Colorado	107	775.8	**421.2**	354.6	423.5	287.3	231.9	191.6
Missouri	106	821.8	**423.3**	398.5	479.5	323.2	212.2	**267.3**
Kentucky	102	**850.7**	**451.4**	399.3	472.5	328.6	185.8	**286.7**
United States	97	844.4	420.5	423.9	506.6	345.2	250.8	255.8
Dist. Columbia	96	**974.4**	**478.8**	**495.6**	**627.1**	**393.1**	**264.0**	**363.1**
West Virginia	88	**846.5**	**451.7**	394.8	467.6	319.2	198.0	**269.6**
Pennsylvania	86	**891.0**	**420.6**	**470.4**	**549.7**	**395.9**	**269.9**	**279.8**
New Jersey	75	**865.3**	401.0	**464.3**	**547.4**	**387.0**	**282.8**	**264.6**
Tennessee	70	**867.8**	**471.7**	396.1	465.9	330.5	171.5	**294.4**
Louisiana	68	**906.9**	**460.4**	**446.5**	**520.9**	**377.0**	242.1	**278.8**
Virginia	65	**914.5**	**444.9**	**469.6**	**561.4**	**383.6**	235.8	**325.6**
Delaware	60	**922.3**	**446.9**	**475.4**	**561.0**	**396.2**	**268.7**	**292.3**
Alabama	55	**917.3**	**491.7**	**425.6**	493.2	**362.2**	177.5	**315.7**
Vermont	53	803.2	392.2	411.0	495.3	333.1	**269.2**	226.1
New York	52	**873.9**	404.2	**469.7**	**550.2**	**395.3**	**336.1**	214.1
Maryland	48	**901.3**	**423.6**	**477.7**	**566.9**	**397.0**	244.6	**322.3**
Washington	44	787.9	387.5	400.4	496.3	308.9	**260.3**	226.0
Arkansas	42	769.8	**421.0**	339.8	399.7	278.3	164.8	234.9
Georgia	41	**927.9**	**471.1**	**456.8**	**554.5**	**370.6**	190.4	**364.1**
Mississippi	39	**950.4**	**549.0**	401.4	448.5	**355.4**	145.2	**303.3**
North Carolina	34	**872.1**	414.3	**457.8**	**553.4**	**370.2**	202.6	**350.8**
Rhode Island	32	836.3	395.0	**441.3**	**539.8**	**356.1**	**316.7**	223.1
New Hampshire	28	802.4	380.3	422.1	**524.9**	328.5	**291.5**	233.4
Massachusetts	23	810.2	379.8	**430.4**	**523.7**	**351.3**	**302.6**	221.1
Connecticut	21	774.9	362.3	412.6	492.0	339.6	**288.4**	203.6
Maine	20	805.7	404.7	401.0	477.8	327.9	246.8	231.0
South Carolina	18	**982.5**	**471.1**	**511.4**	**622.6**	**413.4**	216.6	**406.0**
Oregon	17	764.6	381.2	383.4	464.3	297.4	241.5	222.8
χ^2		10.9	1.7	16.4	11.3	21.7	4.95	11.3
p		<0.01	‖	<0.01	<0.01	<0.01	<0.05	<0.01
r		—0.36	0.02	—0.56	—0.53	—0.58	—0.31	—0.36
p		0.01	‖	<0.01	<0.01	<0.01	0.03	0.01

* Death rate by place of residence. Age-adjusted by direct method to United States total population.[8] Figures in boldface type are those which exceed national average.

† Calculated by average hardness of each supply, surface or ground, times the population served by that supply; the sum of the products thus obtained was then divided by the number of the total population served.[5] Of the total population of the United States, 58.3% was served by these supplies (range 24 to 100% by state).

‡ Category 330-334, 400-468, "International List of Diseases and Causes of Death."

§ Category 420, "Arteriosclerotic Heart Disease Including Coronary Disease," "International List."

‖ Not significant.

RELATION BETWEEN MORTALITY FROM CARDIOVASCULAR DISEASE AND TREATED WATER SUPPLIES

VARIATIONS IN STATES AND 163 LARGEST MUNICIPALITIES OF THE UNITED STATES

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In the United States variations from state to state in death rates from cardiovascular diseases have been unexplained on dietary, racial, or social bases. One variable environmental influence to which all persons are exposed is potable water. Statistical analyses of water hardness and death rates from all causes, cardiovascular diseases, coronary heart disease, and noncardiovascular diseases, showed highly significant correlations for all but noncardiovascular causes. Similar relationships were demonstrated for caucasoid men, aged 45 to 64 years, by state and, in the case of coronary disease, in the 163 largest cities. Of 21 constituents of finished municipal water in each city, highly significant correlations were found for magnesium, calcium, bicarbonate, sulfate, fluoride, dissolved solids, specific conductance, and pH. In all cases correlations were negative, i. e., softer water was associated with higher death rates. Some factor either present in hard water or missing or entering in soft water appears to affect death rates from degenerative cardiovascular disease.

In the United States there are considerable variations from state to state in average age-adjusted death rates from all causes.[1] In general, these variations appear to follow large geographical areas. Thus, in 1949-1951, for which extensive data are available, a national death rate for both sexes of 844.4 per 100,000 population was exceeded in all of the middle Atlantic states, in all of the south Atlantic states save Florida, and in all of the east south central states, thereby giving most of the Atlantic plain and contiguous regions a higher than normal death rate. In other regions, only Illinois in the east north central group, Louisiana in the west south central group, and New Mexico, Arizona, and Nevada in the mountain group had death rates exceeding the national average. In no New England, west north central, or Pacific state was it higher. Extreme rates were 970.5 for Nevada (974.4 for Washington, D. C.) and 712.2 for Nebraska.

Cardiovascular diseases account for a little more than one-half the total mortality in the United States; therefore, similar geographical variations could be expected to exist in death rates from this group of diseases. They do, with notable differences.[2] Thus, a national average death rate in 1949-1951 of 423.4 per 100,000 population was exceeded in Massachusetts and Rhode Island, in all middle Atlantic states, all south Atlantic states except West Virginia and Florida, but in only one east south central state, Alabama. In other regions, the rate in only Illinois, Indiana, and Louisiana exceeded the national average. Extreme rates were 511.4 for South Carolina and 290.2 for New Mexico.

Arteriosclerotic heart disease, including coronary disease, accounts for about 22% of all deaths, about 43% of all cardiovascular deaths, and about 50% of male cardiovascular deaths. Female rates in some areas may be erroneous because of small numbers. A national male rate of 250.8 per 100,000 was exceeded in all New England states except Maine, all middle Atlantic, only two south Atlantic (Delaware and District of Columbia), three east north central (Ohio, Illinois, and Michigan), Nevada, and two Pacific states (California and Washington).[3] Extreme rates were 336.1 in New York and 148.2 in New Mexico, or a difference of more than two times.

These differences are most interesting. In the present state of our social customs, they apparently can hardly be explained on the basis of racial backgrounds, local dietary habits, sources of food, or environmental stresses and strains. Using more exact data, Sauer and Enterline found that they exist for white men aged 45 to 64 years and apparently are real, not being accounted for by inaccurate reporting or by the quality or quantity of physicians.[4] It is possible that some widely variable environmental influence or influences, geographically linked, to which the whole population is exposed, may affect these death rates.

One factor to which all populations are exposed is potable water. Detailed analyses of samples of about 20 constituents and qualities of "finished," or processed, municipal water for 1,315 cities in the United States were made by a United States Geological Survey in 1950-1951.[5] These waters supplied over 90% of the urban and 58.3% of the total population. Wide variations exist in most constituents from state to state and city to city, but geographical trends are evident. Averages for whole states only in hardness of water have been calcu-

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rates in this group of subjects higher than average at the 5% level of significance, while 23 had significantly lower rates.[9] Chi-square analysis with use of a median total hardness of 86 showed a skewed curve significant to less than 1% probability (table 3). As with whole states, the areas with harder water has the lower death rates. Rates varied from 299.0 (Lincoln, Neb.) to 826.8 per 100,000 population (Savannah, Ga.).

In order to discover what constituents of hard water might be associated with this influence on death rates, chi-square distribution about the death rate of the median city and the median of 20 separate constituents or characteristics of water were calculated (table 3). These measurements are routine in analyses done by the United States Geological Survey. In the case of eight constituents of finished water, skewed distributions appeared. In all cases, higher values in water were associated with lower death rates. For other factors no significant distributions were found, especially for color, turbidity, and the number of treatments given water. By inspection of the data it was apparent that no correlation existed with the content of manganese (usually absent) or carbonate (usually absent).

TABLE 2.—*Average Annual Age-Adjusted Death Rates of White Men Aged 45 to 64 Years from Cardiovascular Diseases (per 100,000 Persons), 1949-1951, and Weighted Average Hardness of Finished Municipal Waters, 1950-1951, by State*[*]

State	Hardness† (Ppm)	All Causes	All Causes Except Cardiovascular	Cardiovascular Diseases‡	Coronary Heart Disease	All Other Cardiovascular
South Dakota	299	1,201.1	555.3	645.8	422.1	223.7
Nebraska	247	1,235.6	576.6	659.0	407.0	252.0
New Mexico	237	1,358.7	**795.3**	563.4	316.3	247.1
Indiana	237	1,505.1	667.5	837.6	522.1	**315.5**
Arizona	216	**1,842.9**	**1,063.7**	779.2	435.1	**344.1**
Iowa	212	1,249.9	550.4	699.5	451.2	248.3
Utah	191	1,385.2	673.3	711.9	440.0	271.9
Kansas	176	1,236.2	572.9	663.3	437.5	225.8
Wyoming	171	1,370.0	705.3	664.7	427.2	237.5
North Dakota	170	1,173.2	539.6	633.6	364.5	269.1
Wisconsin	167	1,358.4	607.4	751.0	477.9	273.1
Illinois	156	**1,696.1**	**760.7**	**935.4**	**534.1**	**401.3**
Ohio	150	1,533.6	706.2	827.4	529.8	297.6
Nevada	135	**1,956.3**	**1,015.6**	**940.7**	**576.0**	**364.7**
Texas	132	1,455.0	690.8	764.2	467.7	296.5
Oklahoma	125	1,336.2	632.8	703.4	433.8	269.6
Florida	123	**1,611.2**	**725.3**	**885.9**	**568.4**	**317.5**
Montana	120	1,540.3	**756.0**	784.3	468.6	**315.7**
Idaho	119	1,397.4	663.9	733.5	459.4	274.1
California	118	**1,685.1**	**780.1**	**905.0**	**621.2**	283.8
Michigan	115	1,557.6	**727.1**	830.5	**537.4**	293.1
Minnesota	114	1,261.1	563.8	697.3	442.4	254.9
Colorado	107	1,369.9	699.7	670.2	439.1	231.1
Missouri	106	1,471.2	714.5	756.7	450.2	306.5
Kentucky	102	1,394.8	673.3	721.5	381.0	**340.5**
United States	97	1,563.2	718.2	845.0	534.1	310.9
Washington, D. C.	96	**1,900.7**	**833.0**	**1,067.7**	**622.8**	**444.9**
West Virginia	88	1,474.2	**725.4**	748.8	431.3	**317.5**
Pennsylvania	86	**1,702.9**	**786.2**	**916.7**	**570.0**	**346.7**
New Jersey	75	**1,703.9**	**763.9**	**940.0**	**584.5**	**355.5**
Tennessee	70	1,415.6	669.7	745.9	392.5	**353.4**
Louisiana	68	**1,681.8**	**751.7**	**930.1**	**595.2**	**334.9**
Virginia	65	1,542.2	671.0	**871.2**	**537.0**	**334.2**
Delaware	60	**1,621.0**	**772.1**	**848.9**	**546.7**	302.2
Alabama	55	1,464.8	682.6	782.2	433.4	**348.8**
Vermont	53	1,521.5	712.0	809.5	**550.4**	259.1
New York	52	**1,710.5**	**787.1**	**923.4**	**650.5**	272.9
Maryland	48	**1,716.3**	**760.2**	**956.1**	**580.4**	**375.7**
Washington	44	1,490.9	677.0	813.9	525.7	288.2
Arkansas	42	1,292.2	614.3	677.9	386.6	291.3
Georgia	41	**1,607.3**	702.2	**905.1**	490.1	**415.0**
Mississippi	39	1,455.6	680.0	775.6	437.2	**338.4**
North Carolina	34	1,518.2	603.2	**915.0**	490.1	**424.9**
Rhode Island	32	**1,666.4**	**751.6**	**914.8**	**604.8**	310.0
New Hampshire	28	1,556.9	681.8	**875.1**	**578.9**	296.2
Massachusetts	23	**1,647.7**	**740.5**	**907.2**	**598.6**	308.6
Connecticut	21	1,536.3	706.8	829.5	**551.6**	277.9
Maine	20	1,492.8	687.7	805.1	522.9	282.2
South Carolina	18	**1,816.1**	708.6	**1,107.5**	**616.8**	**490.7**
Oregon	17	1,415.4	659.5	755.9	500.2	255.7
χ^2		4.96	0.99	8.0	9.26	4.6
p		<0.05	§	<0.01	<0.01	<0.05
r		—0.384	—0.10	—0.53	—0.48	—0.40
p		<0.01	§	<0.01	<0.01	<0.01

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[*] Sauer and Enterline.[4] Figures in boldface type are those which exceed the national average.

† Calculated by average hardness of each supply, surface or ground, times the population served by that supply; the sum of the products thus obtained was then divided by the number of the population served.[5] Of the total population of the United States, 58.3% was served by these supplies (range 24 to 100% by state).

‡ Category 330-334, 400-468, "International List of Diseases and Causes of Death."

§ Not significant.

and showed a fairly good correlation between deaths from apoplexy and acidity of river water and a better one between death rates from heart disease and water, according to Japanese prefecture and district.[7] From these data it appears that some quality of water might influence mortality from one or several cardiovascular diseases.

Methods

It seemed rewarding to ascertain what, if any, correlation existed between death rates and known constituents and characteristics of finished water. With use of the data now available, the following three sets of analyses were made: (1) weighted average hardness of water by state (average hardness of each supply multiplied by the population served by that supply, the sum divided by the total number of people served[5] and age-adjusted average death rates by state (male and female, all races) from all causes, from cardiovascular diseases ("International List of Diseases and Causes of Death," categories 330-334, 400-468), from arteriosclerotic heart disease, including coronary disease (category 420), from other cardiovascular diseases, and from all other causes[8]; (2) the same quality of water and age-adjusted death rates by state from these causes for white men aged 45 to 64 years[4]; and (3) 20 constituents of finished water, and age-adjusted death rates for white men, aged 45 to 64 years, from all causes and from arteriosclerotic heart disease, including coronary disease, in each of 163 of the largest metropolitan areas in the United States.[9]

Data on hardness of water by state and death rates were analyzed about their medians by the chi-square method and by determining the coefficients of correlation (r value).[10] Data on the several constituents of water were first analyzed by the chi-square method to detect skewness about median values and then fed into the tape of the Dartmouth electronic computer for analyses of co-variance.

Data on water are listed for each municipality,[5] while those on death rates from coronary heart disease have been compiled for metropolitan areas.[9] In 17 of the latter, data from two or three cities were combined to account for a metropolitan area. Usually each of these had its own water system; therefore, each constituent of water was averaged according to population supplied by the systems, in order to arrive at a mean value per exposed person. When a large city had more than one water system, each constituent was likewise averaged according to the population served.

Death Rates by States and Hardness of Water

Average Death Rates, All Ages and Races and Both Sexes, Age-Adjusted.—Table 1 shows the relationship of weighted average hardness of finished water by states, in order of decreasing hardness, and average death rates from several causes. The water supplies of 25 states showed hardness of more than 97 parts per million, the national average[5]; for 23 states and the District of Columbia water showed less than 97 ppm. Only 5 states in the hard water group, however, had total death rates greater than the national average, while 15 "soft water" states had higher than average rates. This abnormal distribution was significant at a probability of chance of less than 1 in 100 ($p < 0.01$), while the coefficient of correlation was significant at the 1% level. The harder water states had the lower death rates.

Death rates from noncardiovascular causes were equally distributed between hard and soft water areas and there was no correlation found. Therefore, it appeared that cardiovascular death rates might be influenced by hardness of potable water, while death rates from all other causes probably were not. This impression was borne out by an analysis of total cardiovascular death rates. Decided skewness and correlation appeared for total, for male, and for female death rates highly significant (at considerably less than the 1% level).

Similar analysis of male death rates from arteriosclerotic heart disease, including coronary disease, showed skewness ($p < 0.05$) and a correlation ($p = 0.03$) with hardness of water at levels usually accepted as significant, while male deaths from all other cardiovascular diseases were more significantly ($p = 0.01$) correlated with hardness of water. Female death rates were not analyzed, because of inaccuracies inherent in small numbers of cases, but showed similar distributions on inspection. In all these cases, the correlations were "negative," i. e., the harder the water, the lower the death rate.

Tests for significance of distribution by standard errors (u value) showed similar results, death rates from noncardiovascular causes not having and the others having significance, u being more than 3.0 in all cases (more than 2.0 is considered significant).

Average Death Rates for White Men, Aged 45-64 Years, Age-Adjusted.—Rates for this selected group of the population were obtained from Sauer and Enterline's report.[4] Table 2 shows the distribution according to hardness of water. All differences are significant to less than the 5% level, except for noncardiovascular rates, which are equally distributed between hard and soft water areas. Again the correlations are negative, softer water being associated with higher rates, at less than the 1% level of significance.

Death Rates from Coronary Heart Disease and Constituents of Water, by Municipalities

Specific death rates from arteriosclerotic heart disease, including coronary disease, in older white males were compared with the hardness of the finished water in each of 163 large municipalities. Twenty-nine municipalities had adjusted death rates on the sodium and potassium content of water; to all intents this factor was mainly sodium, since little potassium was usually present. Furthermore, the sulfate-bicarbonate ratio was not found significantly correlated, as Kobayashi[6] showed it to be in the case of natural river water and apoplexy; "finished" water is usually treated to reduce acidity by lime or soda ash, followed by carbon dioxide, procedures which alter the ratio considerably. No correlation with the number of different treatments given water was evident; these included softening with lime or soda ash, chlorination, carbonation, sedimentation, filtration, coagulation with ferric sulfate or alum, aeration, adjustment of pH, and the addition of copper sulfate or Calgon. Nor were color or turbidity of water associated with variations in mortality.

Significant negative correlations were found in the cases of water contents of magnesium, calcium, sulfate, fluoride, silica, total solids, and specific conductance (a measure of ionizable minerals in solution). These factors are all related to hardness. In addition, there was a significant negative correlation with bicarbonate which reflects contact with carbonate rocks as well as aeration and decaying vegetable matter, and can alter pH, and with "noncarbonate hardness."(Noncarbonate hardness refers to the quantities of calcium and magnesium sulfates, chlorides, or nitrates in solution).[5]

The pH of the finished water varied widely from city to city, from an extreme low of 3.9 (Altoona, Pa.) to an extreme high of 10.4 (Oklahoma City); there were four cities with a finished water pH of less than 6.0 and 20 with a pH of 9.0 or more. The correlation was again negative; i. e., alkaline waters appeared to "protect" at about the 1% level of significance. This finding is along lines of agreement with those of Kobayashi.[6]

The meaning of this apparent influence on cardiovascular death rates is unclear, but a modicum of speculation is in order. The data suggest one of three possibilities: 1. There is something "beneficial" to the outcome of cardiovascular disease in hard waters. 2. There is some adverse factor in soft waters. (The amount of dietary calcium and magnesium contributed by water to total nutritional requirements is relatively small. For a daily intake of 800 mg. of calcium, 2 liters of water would supply 2 to 280 mg. [mean, 60 mg.] in these municipalities. For an intake of 240 mg. of magnesium, 2 liters of water would supply 1 to 88 mg. [mean, 20 mg.]. Deficiency of these two essential minerals induced by soft water therefore appears unlikely.) 3. Soft waters and acid waters attack the pipes through which they run, taking up zinc, cadmium, iron, copper or lead, depending on the kind of pipes and solders used. In that event, cadmium or lead might be suspect; both accumulate in human tissues. (Cadmium has been demonstrated by this laboratory in samples of several soft waters standing or running through galvanized iron pipes, at concentrations of 0.2 to 2.1 mcg. per liter, while copper has been found in taps supplied by copper pipes at concentrations of 0.03 to 1.4 mg. per liter).

The question naturally arises: Does modern water treatment have anything to do with this variation in death rate? Or, perhaps, with the apparent increase in cardiovascular mortality during the past 50 years? Municipal treatment of water is relatively new. In 1932 a report on 670 municipalities showed only 40 furnished with softened water, representing 7.2% of the urban and 3.4% of the total population of the country.[5] In 1952, of 1,315 municipalities 171 had softened water, representing 16.5% of the urban and 9.6% of the total population of the country. This relatively small increase, which does not include the many areas with naturally soft water, could hardly affect death rates very much. Almost all water considered in this report was chlorinated, a practice usual for many years of this century. For industrial purposes, pH of water is usually adjusted toward the alkaline side in order to minimize corrosion.

TABLE 4.—*Summary of Correlations of Weighted Average Hardness of Water, 1950-1951, and Average Annual Death Rates from Various Causes, Age-Adjusted, 1949-1951, by State*

Cause of Death	U. S. Rate Per 100,000 Persons	χ^2	p	r	p
All Ages					
All causes	844.4	10.9	<0.01	−0.36	0.01
All causes but cardiovascular	420.5	1.7	*	+0.02	*
Total cardiovascular	423.9	16.4	<0.01	−0.56	<0.01
Male	506.6	11.3	<0.01	−0.53	<0.01
Female	345.2	21.7	<0.01	−0.58	<0.01
Coronary heart disease Male	250.8	4.95	<0.05	−0.31	0.03
All other cardiovascular Male	255.8	11.3	<0.01	−0.36	0.01
White men, aged 45-64 years					
All causes	1563.2	4.96	<0.05	−0.384	<0.01
All causes but cardiovascular	718.2	0.99	*	−0.10	*
Cardiovascular	845.0	8.0	<0.01	−0.53	<0.01
Coronary heart disease	534.1	9.26	<0.01	−0.48	<0.01
All other cardiovascular	310.9	4.6	<0.05	−0.40	<0.01
All ages					
Malignant neoplasms (1957)	148.7	1.25	*	...	...
Motor vehicle accidents	23.1	4.58	<0.05	...	...
Vascular diseases of central nervous system	194.9	5.13	0.03	...	...
General arteriosclerosis	12.3	7.58	<0.01	...	...
Hypertension with heart disease	123.6	18.13	<0.01	...	...

* Not significant.

For several years reasons for the wide geographical variation in death rates from cardiovascular diseases in this country have been discussed speculatively, according to prevailing fashions of etiological thinking. This report does not solve the problem, nor does it suggest definite causes for one or more of this group of degenerative diseases. For the first time, however, a definite clue is provided; when followed, this clue may lead to definition of an environmental influence which affects adversely the course of coronary heart disease, hypertension, In order to define some of these correlations more exactly, data on 16 constituents of water were fed into an electronic computer for calculation of co-variance with both total and coronary death rates. The results are shown in table 3. Negative correlations significant to a level of less than 1 chance in 100 were found for concentrations of calcium, magnesium, bicarbonate, and sulfate and for total solids and hardness as related to death rates from coronary heart disease. Death rates from all causes were also significantly related to total hardness of water. When the effect of hardness was removed mathematically from the analytical data, significant correlations disappeared, suggesting that there was no measured "hidden factor" in hardness. No significant correlations were found with death rates and sodium plus potassium, chloride, the sulfate-bicarbonate ratios, iron, or nitrate, but those significant at about the 1% level appeared for fluoride, pH, and specific conductance, and at about the 2 and 3% level for noncarbonate hardness and silica. Values of pH varied independently of several factors making up hardness.

TABLE 3.—*Correlation of Constituents of Finished Water, 1950-1951* and Death Rates from Coronary Heart Disease in 163 Metropolitan Areas of the United States of White Men, Aged 45-64 Years, 1949-1951†*

Coronary Disease and Water Constituents	Chi-Square Distribution				Coefficient of Correlation	
	Ppm		Chi-Square	p	r	p
	Mean	Median				
Silica (SiO_2)	10.3	7.0	0.72	...	−0.188	0.03
Iron (Fe)	0.12	0.07	0.221	...	−0.051	...
Manganese (Mn)	—	...	...	...	...	...
Calcium (Ca)	31.1	23.0	5.19	<0.05	−0.27	<0.01
Magnesium (Mg)	9.75	6.2	7.07	<0.01	−0.30	<0.01
Sodium and potassium	21.7	8.0	3.27	...	−0.01	...
Carbonate (CO_3)	—	...	...	...	...	...
Bicarbonate (HCO_3)	98.1	55.0	7.53	<0.01	−0.21	0.01
Sulfate (SO_4)	43.9	26.0	3.847	0.05	−0.22	<0.01
SO_4:HCO_3	0.98	0.39	0.155	...	−0.035	...
Chloride (Cl)	20.1	8.0	3.836	0.05	−0.02	...
Fluoride (F)	0.25	0.1	1.26	...	−0.207	0.01
Nitrate (NO_3)	2.3	1.2	3.02	...	−0.144	...
Dissolved solids	210	137	6.44	<0.02	−0.22	<0.01
Hardness as $CaCO_3$, total	117.7	80	12.11	<0.01	−0.29	<0.01
Noncarbonate	38.7	25	2.22	...	−0.198	0.02
Color	4.2	3	0.07	...	...	...
pH	7.08	7.6	6.36	<0.02	−0.204	0.01
Specific conductance (micromhos at 25C)	327	270	9.19	<0.01	−0.207	0.01
Turbidity	1.5	1.0	0.01	...	...	...
Number of treatments	4.9	6	0.05	...	...	...
All causes of death and hardness	...	...	...	...	−0.33	<0.01

* U. S. Geological Survey.[5]
† Enterline and co-workers.[9]

Comment

From the data it becomes apparent that mortality from cardiovascular and coronary heart diseases from state to state and city to city was influenced from 1949 to 1951 by some constituents of finished municipal water with which hardness was associated. It is also apparent that during the same period mortality from all other causes was not so influenced.

About 43% of all deaths (and one-half the male deaths) caused by diseases of the cardiovascular system are accounted for by arteriosclerotic heart disease. The remaining 57% comprised the following diagnoses in 1949 to 1951[11]: vascular lesions affecting central nervous system (21%), general arteriosclerosis (4%), hypertension (13%), other circulatory diseases (1%), rheumatic heart disease (3%), and a group of miscellaneous heart diseases (14%). Of these, the degenerative cardiovascular diseases form a large majority, not only in older men (90%) but in all ages (90%). Therefore, the correlation of degenerative cardiovascular diseases (including hypertension) with softness of water appears evident.

In order further to check the results, chi-square distribution was tested on other major causes of death, using 1957 rates.[11] No correlation with hardness of water was found for malignant neoplasms, vascular lesions of the central nervous system, nor general arteriosclerosis by total death rates. However, the simple test disclosed a correlation of hardness and rates in persons 55 to 64 years of age (during 1949 to 1951) for hypertension ($p < 0.01$), general arteriosclerosis ($p < 0.01$) and vascular lesions of the central nervous system ($p = 0.03$), in soft water states having lower rates. Death rates from motor vehicle accidents were higher in hard water areas ($p < 0.05$) while those from other accidents showed no correlation. This last finding is unexplained. The rates are relatively small and may not be reliable for more exact analysis.

Several surprising results have come out of this study. First, the high degrees of significance of most of the correlations surpass considerably the usually accepted statistical level (5%) of most biological experiments (table 4). The levels of significance found are strong evidence that relationships are real and not the result of some remote "fluke"; there are more than 99 chances in 100 that 15 out of 18 of these correlations are not accidental. Second, the correlations are all opposite to the direction suspected by superficial thinking or "snap judgment," i. e., hard water was associated with "protection." In fact, analyses were set up with the opposite results, if any, in view. Third, correlations held true not only for death rates for all ages and races, but for a selected group of white men, and in the case of coronary heart disease, for cities as well as for states. Fourth, correlations were good or excellent for all cardiovascular diseases, for male coronary heart disease, and for other male cardiovascular diseases and softness of water. Proof of association lies in the lack of correlation of water hardness and deaths from all other causes.

Attempts to define further what influences in water hardness might be associated with lower than normal death rates were successful mainly in excluding several factors. The influence on cardiovascular mortality appeared not to depend on the amounts of iron, manganese, carbonate, or nitrate. Nor was there apparent dependence of death

THROMBOCYTOPENIA INDUCED BY ADMINISTRATION OF SODIUM PARA-AMINOSALICYLATE

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A 63-year-old man developed thrombocytopenia while being treated with streptomycin, isoniazid, and sodium para-aminosalicylic acid (PAS) for active pulmonary tuberculosis. He had no history of previous allergic manifestations. He had recently developed mild diabetes and suffered a crushing injury of the left hand. In order to determine which of the medicaments caused the thrombocytopenia, test doses of each were administered to the patient after his platelet count had returned to normal. A severe decrease in platelet count occurred one hour after administration of PAS; it did not occur when the other drugs were administered. Concurrent administration of cortisone with PAS apparently had no effect on the thrombocytopenia. This is believed to be the second reported instance of thrombocytopenia in which PAS proved to be the offending agent.

Hypersensitivity reactions to para-aminosalicylate (PAS) are well known, and numerous reports in the medical literature have discussed such reactions as hepatitis, dermatitis, hemolytic anemia, granulocytopenia, nonthrombocytopenic purpura,[1] Löffler's syndrome, neutropenia, serum-sickness-type reactions, and a clinical picture resembling infectious mononucleosis.

One of us (R. L. M.) with Wurzel[2] reported the syndrome of thrombocytopenic purpura due to administration of PAS and confirmed this observation by readministration of the drug. Although other physicians[3] have noticed the occurrence of this phenomenon in patients receiving both streptomycin and PAS, no attempt was made to ascertain which of the two drugs was responsible for the reaction. This case is believed to be the second instance of thrombocytopenia after the use of PAS in which PAS was proved the offending agent. An attempt was made to modify the experimentally induced thrombocytopenia in this patient by the use of cortisone.

Report of a Case

A 63-year-old man was admitted to the tuberculosis ward of the Philadelphia General Hospital on Aug. 8, 1956, with known active pulmonary tuberculosis. The patient had been treated at home since 1953 by his family doctor after the demonstration of a cavity in the apex of his left lung. Medication during this interval had consisted of administration of streptomycin, 1 Gm., three times a week, and PAS, 12 Gm. per day, until the time of admission to the hospital. Results of gastric cultures, which had been negative since 1955, were positive one month prior to admission to the hospital. One week before admission, the patient was hospitalized at another institution for a crushing wound of the left hand, necessitating tendon repair; at that hospital routine laboratory studies showed a hemoglobin concentration of 9.8 Gm.% and a leukocyte count of 5,900 per cubic millimeter, with a normal differential count. The patient was transferred to this hospital for further therapy of his tuberculosis.

His medical history was not remarkable except for pulmonary tuberculosis and a herniorrhaphy which had been done several years previously. There was no history of any allergic manifestations or previous drug allergies.

At the time of admission physical examination revealed a well-developed, well-nourished man in no acute distress. Blood pressure was 135/80 mm. Hg; temperature, 99 F (37.2 C); pulse, 88 per minute; and respirations 16 per minute. Pertinent findings consisted of a crush wound of the left hand with a scar on that hand from a recent operation; grade 2 arteriosclerotic retinopathy, dulness to percussion at the left apex and a decrease in breath sounds, tactile fremitus, and vocal fremitus in this area. There was a scar from operation in the lower left quadrant, and rectal examination revealed slight prostatic enlargement with several small external hemorrhoids.

Laboratory studies showed the following results: hemoglobin level, 9.8 Gm.%; leukocyte count of 6,700 per cubic millimeter; hematocrit 33% volume of cells. No differential count was performed at the time of admission. Results of urinalysis revealed a specific gravity of 1.023, 2+ sugar and 2+ albumin. The serologic tests for syphilis were nonreactive; the blood urea nitrogen level was 41 mg.%; and the fasting blood-sugar level was 249 mg.%.

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and atherosclerosis, which three entities account for most of the degenerative cardiovascular disease in the United States today.

Summary

Analyses of death rates by state in the United States for the years 1949 to 1951 and certain characteristics of public water supplies were made. Significant negative correlations were found between mean hardness of finished water weighted for population and total mortality, cardiovascular mortality (total, male and female), male mortality from coronary heart disease, and male mortality from all other cardiovascular diseases. No correlations between hardness of water and noncardiovascular deaths were found. For white men aged 45 to 64 years, highly significant negative correlations were found between hardness of water and total death rate, cardiovascular mortality, mortality from coronary heart disease, and from other cardiovascular diseases. There was none for noncardiovascular disease.

Analyses of total death rates and mortality from coronary heart disease in white men aged 45 to 64 years in 163 municipalities again showed highly significant negative correlations with total water hardness. Applying the data to 20 other constituents and characteristics of finished water, highly significant negative correlations were found with contents of magnesium, calcium, bicarbonate, sulfate, fluoride, and dissolved solids, the specific conductivity of water, and especially with pH. Correlations were significant in the cases of silica and noncarbonate hardness. In all cases, higher values were associated with lower death rates.

No significant correlations between death rate and 10 other factors in finished water were found: silica, iron, sodium and potassium, chloride, the ratio of sulfate to bicarbonate, nitrate, manganese, carbonate, color, turbidity, or the number of treatments given water. The data offer a clue to an environmental influence associated with the nature of public water supplies which affects adversely the course of degenerative cardiovascular diseases in the United States.

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SIGNIFICANCE OF MINOR INFECTIONS.—It is a gross error to minimize the epidemiologic importance of so-called minor infections, for example a stitch abscess. The same strain may kill the next patient. Therefore, one must use all possible precautions to prevent transfer of the organisms to another patient. To identify the source of an infection, typing the strains with bacteriophage is the only accurate method available at present. However, typing of a strain has no clinical or prognostic value. Typing is only of epidemiologic value. Furthermore, only about 60 per cent of the strains are susceptible to the bacteriophages presently in use. . . . Reduction of the number of infections acquired within a hospital to a minimum requires the rigid application of aseptic technic by all persons having contact with patients. Each person must always act as if he were a carrier even though a transient one, because he may be.—L. A. Weed, Ph.D., M.D., Epidemiology of Staphylococcal Infections, *Anesthesia and Analgesia*, January-February, 1960.

As a control, the experiment was again repeated two weeks later without cortisone (fig. 3) and with doses of 1 and 1.5 Gm. of sodium PAS, respectively, on the second and third day of the test. During this test the degree and duration of thrombocytopenia was not as marked as on either of the previous tests in spite of the fact that larger doses were used.

All platelet counts were taken by the method of Rees-Ecker, with blood collected in dried oxalated tubes, and all determinations were made within 15 minutes after the sample was collected.

Blood was collected for platelet agglutination studies with siliconized syringes and needles and placed in siliconized tubes. Samples were collected just prior to the first provocative test with PAS. and two days later when the platelet drop was maximal. Another sample was collected during the test with cortisone two days after administration of the PAS, at the time when the platelet drop was greatest. The platelet agglutinins were determined according to the method of Stefanini and Dameshek[4] and in addition Coombs' technique applied to the platelets was used. The platelet agglutinin studies were repeated with the addition of a 1% solution of PAS. No agglutination was demonstrable in any of the specimens.

Comment

The role of PAS as the agent responsible for this man's thrombocytopenic purpura has been well established by the provocative studies. The fall in the platelet count observed in patients with drug-induced thrombocytopenic purpura usually occurs within 60 to 90 minutes after the administration of the offending agent and the amount necessary to produce the effect is usually small, although in the patient of one of us (R. L. M.) with Wurzel,[2] administration of a 4-Gm. dose was necessary to produce significant thrombocytopenia. The wide range of dosage necessary to reproduce a reaction has been well shown by Bolton and Dameshek[5] who found that, with quinidine, provocative doses of from 15 to 1,000 mg. were necessary to produce thrombocytopenia, and that some persons developed sensitization with as little as 0.8 Gm. of quinidine over a four-day period. One patient had three episodes of thrombocytopenic purpura during a seven-year period with intermittent administration of the drug. Our patient had received PAS continually for three years prior to developing the thrombocytopenia, and it is difficult to understand why sensitivity should be so late in developing. It is possible that the crush injury of his hand in some way contributed to this late development of sensitivity.

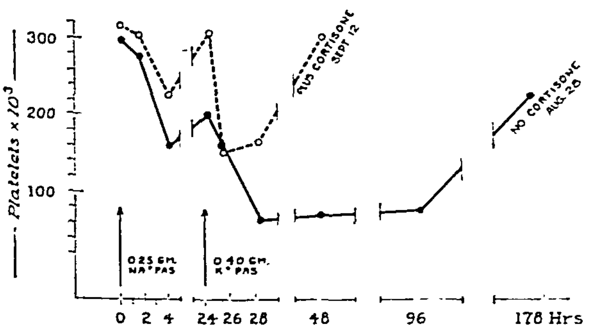

Fig. 2.—To confirm impression that thrombocytopenia was due to PAS, test doses indicated above were given on Aug. 28 and 29. Marked fall confirmed impression that PAS was offending agent. When cortisone was given before and during test doses of Sept. 12 and 13, less fall was noted.

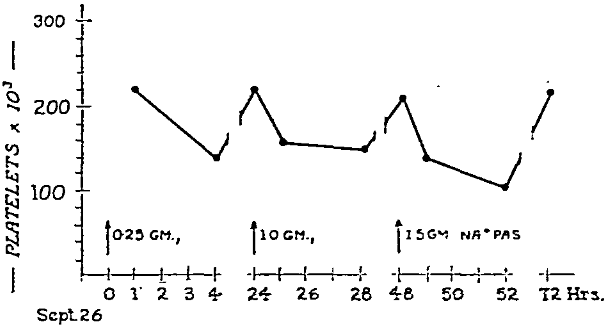

Fig. 3.—Two weeks after test with cortisone, fall in platelets after even larger doses of PAS was less and of brief duration. This would indicate decrease in hypersensitivity due either to passage of time or to prolonged cortisone effect.

The rapid fall in the platelet count indicates that the most likely mechanism was one of platelet sequestration or destruction rather than a failure of formation. This may have been due either to platelet agglutination, to lysis, or to both. The marrow picture of either megakaryocyte arrest or platelet destruction is similar and therefore of no help. The PAS probably acted as a hapten and combined with the platelets to form an antibody similar to the mechanism described by Landsteiner[6] in his azoprotein antigen studies. Such a theory has been shown by Ackroyd[7] to be operative in purpura due to therapy with allyl-isopropylacetylcarbamide (Sedormid). He also demonstrated that agglutination can occur without complement,[8] but that platelet lysis is dependent on it, and succeeded in isolating the lytic factor from the serum of a patient with "Sedormid purpura"[9] by dialysis of the platelets containing the antibody, or, by washing the platelet antibody combination with a saline solution. Bigelow and Desforges[10] reported two patients with thrombocytopenic purpura associated with quinidine therapy and showed that the patient's serum, to which quinidine had been added, produced platelet agglutination. Bolton and Young,[11] using quinidine, quinine, and sulfamethazine, known to have caused thrombocytopenic pur-

The patient continued taking his previous medicaments for tuberculosis until sensitivities of his organism to antibiotics could be determined. His newly discovered diabetes was controlled by diet and treatment with NPH (isophane) insulin. Planograms of the left upper lobe revealed a small cavity in the left apex. On the 10th day of hospitalization, the patient began to bleed from the rectum and this was, at that time, attributed to the presence of external hemorrhoids. However, the next morning, the patient's temperature rose to 104 F (40 C), and he developed spontaneous epistaxis, hematemesis, and melena. Purpuric lesions were found on his extremities and, to a lesser extent, on his torso. During the next three days, hematemesis in amounts measuring 50 to 200 cc. occurred with continued melena and epistaxis. During the four days after his initial hemorrhage, the patient was given a total of 3,000 cc. of whole blood. All medication was discontinued except for 100 mg. of cortisone intravenously at the onset of the bleeding, followed by 300 mg. of cortisone intramuscularly daily for three days, at which time his hematemesis had ceased and his medicament was given by mouth. No change in the chest roentgenogram occurred during and subsequent to this period. Laboratory studies on the second day after the onset of the purpuric phenomena (11th hospital day) revealed: leukocyte count, 11,800 per cubic millimeter, with a differential count of 74% polymorphonuclear leukocytes, 11% lymphocytes, 14% eosinophils, and 1% monocytes. The bleeding time was 8 minutes and 10 seconds; clotting time 3 minutes, 42 seconds; the prothrombin time (Quick method) 54% of normal (19 seconds); hemoglobin level 6.2 Gm.%; and platelets 12,000 per cubic millimeter. Results of urinalysis revealed 5 to 15 red blood cells per high-powered field. Results of cold agglutination and direct Coombs tests were negative. An iliac crest marrow aspiration performed on the 12th day of hospitalization showed slight marrow hyperplasia with an increase in the M:E (myeloid:erythroid) ratio, toxic granulation of the neutrophils, normal megakaryocytes, and an absence of platelets. From the 11th to the 15th hospital day, the platelet count rose gradually from 12,000 to 54,000 (fig. 1), with cessation of the hemorrhagic diathesis by the 15th hospital day and return of the bleeding time and temperature to normal. The dosage of cortisone was gradually decreased and finally stopped by the 20th hospital day. The platelet count had returned to normal (316,000) on the 23rd hospital day and the blood eosinophil level reached a maximum of 22% per cubic millimeter on the 13th hospital day, with a return to normal by the 18th hospital day. Six months later, his left upper lobe was successfully resected and he was discharged from the hospital one year later as having inactive tuberculosis.

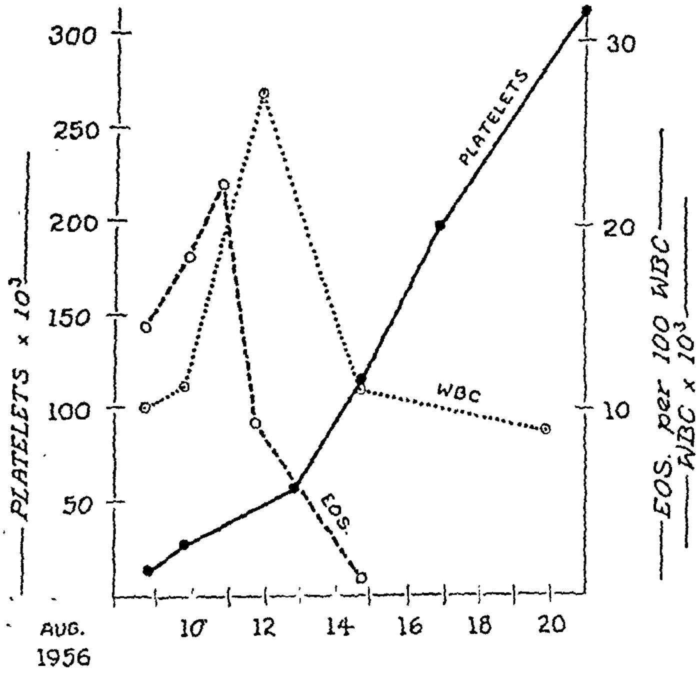

Fig. 1.—Changes in platelet count, total white cell count, and eosinophil count after discontinuation of para-aminosalicylate therapy in patient.

In order to determine which of the medicaments was responsible for the thrombocytopenic purpura, test doses of each were administered. On the 23rd hospital day, 0.5 Gm. of streptomycin was given and continued in doses of 1 Gm. two times a week without incident and with no change in the platelet count. Administration of isoniazid was begun in doses of 100 mg., three times a day, and continued throughout the remainder of his hospital course. On the 29th day, 0.25 Gm. of sodium p-aminosalicylate was given orally after a base-line platelet determination and with platelet counts taken at one-hour and four-hour intervals subsequently. The next day 0.4 Gm. of potassium p-aminosalicylate was administered orally and platelet counts were taken at similar intervals. A decrease in the platelet count was noticed in the specimen taken one hour after administration of the drug on both occasions, with a maximum drop to 41,000 per cubic millimeter four hours after its administration on the second occasion. There was no evidence of hemorrhage or purpura. Two days later the platelet count was still only 46,000 per cubic millimeter but rose to normal by the 35th day of hospitalization (fig. 2).

We next attempted to determine whether or not cortisone administered prior to and during the administration of p-aminosalicylate would either prevent or modify the development of thrombocytopenia. Cortisone was administered by mouth in a dose of 100 mg., four times a day, for four hours, prior to the day of, and during trial therapy with PAS. It will be noted (fig. 2) that the degree of thrombocytopenia was not as marked, nor was the duration as long after the use of cortisone.

ANESTHETIC MANAGEMENT OF PENETRATING WOUNDS OF THE HEART

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A study was made of the types of anesthesia chosen by the anesthesiologists in 100 cases of penetrating wounds of the heart. The most urgent problems were hypotension due to loss of blood, cardiac tamponade due to hemopericardium, and hypoxia due to pneumothorax or hemothorax. In 47 cases no preoperative medicaments were given; nearly all the other patients received atropine or scopolamine. Cyclopropane, with or without other anesthetics, was used in 74 cases because of the quick, quiet induction it afforded. Intubation of the trachea was done as soon as possible, to assist respiration, and then thoracotomy in order to relieve cardiac tamponade or to stop hemorrhage. Four patients who were moribund when admitted to the hospital received only oxygen, and there were eight other deaths. The average length of hospitalization for this group of patients was 14 days.

Many physicians are familiar with wounds of the thorax sustained in war. Fewer realize the significance of similar wounds which may be incurred in a civilian population. Gunshot wounds of the chest can occur while hunting or during inexpert cleaning of a gun in the home. Knife wounds of the thorax are often seen as a result of physical violence in densely populated urban areas; other penetrating injuries may result from sudden deceleration on the highways. In a large municipal hospital, it is not unusual for several patients to be admitted with severe thoracic injuries in a 24-hour period.

Most patients with penetrating injuries of the heart fall into two groups, (1) those with extensive lacerations or large-caliber gunshot wounds of the myocardium, with rapid, massive blood loss, who die almost immediately, and (2) those patients who develop cardiac tamponade and who subsequently undergo cardiorrhaphy. It is the altered physiology and anesthetic management of this latter group with which we are concerned.

Historical Review

Much has been written on penetrating wounds of the heart and statistics from this clinic, as well as other large municipal hospitals, have been reported. Cooley and Brockman[1] studied factors which influence survival in experimental cardiac tamponade and have contributed a tremendous amount to our knowledge of the pathological physiology involved. Little has been written, however, on the anesthetic management of the patient with cardiac tamponade who arrives in the operating theater for cardiorrhaphy.

Up to the end of the last century, penetrating wounds of the heart were considered hopeless. Even Billroth, who dominated the surgery of his time, refused to treat these unfortunate patients[2] and only 80 years ago denied permission for paracentesis of the pericardium. There were many physicians before and after Billroth who did not share the opinions of their contemporaries and investigated ways of treating patients suffering from cardiac trauma. Four hundred years ago, the French surgeon, Ambroise Paré, claimed that wounds of the heart may heal.[2] Dominique Jean Larrey, another French surgeon during the Napoleonic era, reported spontaneous recoveries and treated cardiac wounds by pericardial aspiration.[2]

Bonetus in 1700 and Morgagni in 1730 established the fact that a sudden filling of the pericardial sac arrested heart action and that wounds of the heart were not necessarily immediately fatal.[3] In 1761, Morgagni[4] punctured a coronary artery and demonstrated cardiac tamponade, thus pointing out the main danger in cardiac trauma. In 1882, Block sutured heart wounds in rabbits,[5] and in 1895, DelVecchio made a wound in the heart of a dog, which he successfully closed.[5] He suggested the method be used in operation on man. It was not until 1896 that Rehn[6] of Germany reported the first repair of a laceration of the heart in which the patient survived operation. Eleven years later he reported a series of 124 patients operated on for injuries of the heart, with a recovery rate of 40%.[7] Many of these patients died from infection. Little reference is made to the type and technique of anesthesia that was used at that time.

Apparently local anesthesia was used in most cases. However, as early as 1907, Rehn advised inflation of the lungs by a pressure difference apparatus.[7] Circulation was supported by administration of isotonic sodium chloride solution, to which a few drops of epinephrine were frequently added.[7] Since these early reports, general knowledge and techniques have improved rapidly. The establishment

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pura previously in their group of patients, were able to demonstrate a similar mechanism. Agglutination and lysis were seen in two patients and agglutination only occurred in the third. Bolton[12] was able to demonstrate the importance of the anticoagulant used in effecting the type of reaction obtained during the platelet serologic studies with quinidine. Heparinized blood was found to give only slight platelet agglutination, followed by rapid lysis of the platelets; whereas when citrate was used as an anticoagulant, it produced agglutination with a minimal degree of lysis later. Samples collected in ethylenediamine tetraacetic acid (Sequestrene) revealed strong agglutination, but no lysis. The differences in the results were ascribed to the anticomplementary nature of the anticoagulant and possible variation in human complement.

Using paper electrophoresis, Tullis[13] isolated a platelet antibody in the gamma-globulin fraction of patients with thrombocytopenic purpura, unrelated to drug hypersensitivity, as did Bolton,[12] in patients with purpura secondary to quinidine therapy.

Perhaps our most interesting observations were those obtained in studying the effects of cortisone (fig. 2 and 3). The first challenge without cortisone on Aug. 28th showed a marked, prolonged platelet drop; when repeated on Sept. 12th after administration of cortisone, the effect was less pronounced. At this point it was believed that cortisone might have interfered with the thrombocytopenic effect. However, a repetition of the test without use of cortisone on Sept. 26th showed an even greater loss of effect. It is possible that some long-term interference with the system occurred after cortisone administration; however, it seems more likely that this result may have been due to a loss of sensitivity occurring with the passage of time since the patient had had 20 days of cortisone therapy prior to the first test.

It is interesting to speculate that this decrease in sensitivity to PAS may have occurred because the repeated small doses of PAS had served partially to desensitize the patient. Hayes and Weiss,[3] assuming that PAS had been the agent responsible for the thrombocytopenia in their patient, claimed that they successfully desensitized their patient to PAS with no untoward reaction while maintaining streptomycin therapy.

The fact that we were unable to demonstrate platelet agglutinins or platelet lysis is somewhat disturbing, but other laboratories using the same technique have also been unable to demonstrate either reaction in drug-induced thrombocytopenic purpura.

Although Landsteiner[6] demonstrated in his azo dye experiments that a high concentration of hapten would inhibit his precipitin reaction, no such mechanism is operative in demonstrating platelet agglutination with quinidine and is presumed not to have been operative in our case.

Summary

Thrombocytopenic purpura with massive gastrointestinal hemorrhage was observed in a patient receiving sodium PAS and streptomycin. The causative role of the PAS was demonstrated by recurrence of the thrombocytopenia after the readministration of PAS.

Administration of cortisone concurrently with PAS was accompanied by decreased thrombocytopenia; however, this was believed to be due to the lapse of time rather than an effect due to treatment with cortisone.

Dr. Harold Wurzel performed the platelet agglutination studies and reviewed this manuscript.

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and co-workers, in experiments on dogs, tested the animals' tolerance to increased pericardial pressure after increasing the blood volume by a rapid intravenous injection of isotonic sodium chloride solution. In his experiments, it was shown that dogs so treated were able to tolerate a much higher intrapericardial pressure. Cooley[12] demonstrated that rapid injection of about 300 cc. of saline produced a slight but exceedingly transient rise in blood pressure. This had previously been demonstrated by Beck[13] and Sawyer.[14] It appears that further increase in venous pressure by means of saline or blood infusions apparently enhances cardiac filling, in spite of the associated elevation of pericardial pressure which is produced.

The dramatic improvement of these patients, after aspiration of only 50 to 100 cc. of fluid from the pericardial sac, cannot be overemphasized.[9] A critical level of pericardial pressure and volume of intrapericardial fluid will be reached if aspiration is not done. Beyond this critical pressure, circulatory arrest will occur. As these patients are admitted, intravenous infusions of either saline or blood are started, but no attempt is made to correct the shock with massive transfusions prior to the induction of anesthesia. The tamponade is relieved either by aspiration or by immediate thoracotomy and direct aspiration of the tamponading fluid.

Anesthetic Management

To the anesthesiologist, these patients present a particular challenge. The most serious immediate problems are those of hemorrhage and cardiac tamponade. In addition, the already existing hypoxia is aggravated by a coexisting pneumothorax or hemothorax which impairs respiration. Respiratory acidosis may result from the uneven ventilation and the slowed circulation. The collapse of the pulmonary and systemic circulations prolongs the absorption and distribution of any gaseous or intravenous agent which may be selected. A remarkably high percentage of these patients will have consumed a full meal or more than enough fluid, with or without a high alcohol content, immediately prior to injury. Not only does this alcoholic type of premedication hinder in obtaining full cooperation of the patient, but it has been shown that alcohol, which is a central nervous system depressant and peripheral vasodilator, significantly decreases an animal's tolerance to cardiac tamponade.[12]

The effects of artificial pulmonary ventilation on the patient in cardiac tamponade is no less important. Experimentally it has been shown that alternating positive pressure of the lungs produces further increase in pericardial pressure and venous pressure, whereas alternating positive-negative pressure insufflation appears to enhance cardiac filling. That we have encountered no difficulty, or, perhaps more accurately, have not recognized any difficulty, from these circumstances in patients with tamponade, is probably due to the rapid thoracotomy, quick relief of the tamponade, and cardiorrhaphy.

In this study of 100 patients, 94 were anesthetized for thoracotomy. In 47 patients, no preoperative medication was given. Only atropine or scopolamine (0.4 mg.) was given in 46 patients. Seven patients received both a belladonna derivative and a narcotic, morphine (10 mg.) or meperidine (50 to 75 mg.).

The induction of anesthesia is a particularly crucial period. Coughing and breath-holding, with or without vomiting, aggravate the preexisting hypoxic condition. In addition, the slowed circulation does not favor a rapid induction of anesthesia. A reasonably rapid and quiet induction can be accomplished with cyclopropane. Intubation of the trachea should be done as soon as possible. This will insure more adequate inflation of the lungs, as well as protecting against possible aspiration. However, thoracotomy should not be delayed until intubation has been performed. Oxygenation of the blood can be accomplished with only a mask, a rebreathing bag, and a source of oxygen. The urgency of decompression of the tamponade and the impending circulatory failure make it imperative to ventilate the patient immediately; the endotracheal tube can be introduced after a few minutes, when the circulation is more stable. In most cases, intubation of the trachea was performed, aided by a small amount of intravenous succinyldicholine.

TABLE 2.—*Type of Anesthesia Used in Ninety-four Patients*

Agent	Patients, No.
Cyclopropane	41
Cyclopropane plus muscle relaxant	20
Cyclopropane plus ether	13
Nitrous oxide plus barbiturate or relaxant	13
Thiamylal sodium plus cyclopropane	3
Oxygen only	4

In table 2 it is shown that cyclopropane was the preferred agent in 74 cases in this clinic. This particular agent has many advantages which make it particularly adaptable to this type of "poor risk" patient. It causes the least disturbance to the compensatory mechanisms to blood loss, and cyclopropane depresses myocardial contractile force less than some of the other commonly used agents such as ether and the barbiturates. In addition to a reasonably rapid induction, it can be eliminated quickly and it facilitates controlled respiration, even in a patient under light anesthesia.

It has been proved that cyclopropane prevents the occurrence of hypotension during raised airway pressure.[15] Anesthesia induced with this agent is accompanied by elevation of intrathoracic and right atrial pressures. This increase in intrathoracic and of blood banks, the development of chemotherapeutic and antibiotic agents, and the advances that have been made in anesthesia have made surgery of the traumatized heart more successful. Certainly the introduction of endotracheal techniques, the advent of new anesthetic agents and relaxants, as well as the knowledge of the physiology and treatment of cardiac tamponade, have played a part in the reduction of mortality from penetrating wounds of the heart.

Present Study

As in any other big city hospital, injuries to the heart are seen frequently at the Detroit Receiving Hospital. During the last nine years, 100 patients have been admitted to this clinic with known intrapericardial wounds. This review includes 8 women, all of whom recovered, and 92 men, 12 of whom died. The causes of death will be evaluated later. The oldest patient was 76 and the youngest 15 years of age. Most of the injuries were stab wounds inflicted by knives (89%); some injuries were caused by ice picks (5%) and some by gunshot wounds (6%). Of these 100 patients, 94 were treated by thoracotomy and cardiorrhaphy, 5 by pericardicentesis only, and one was not treated. The five patients treated by pericardicentesis only were in good condition on admission. One patient died in the emergency room before any therapy could be initiated, and unfortunately no cardiac resuscitation was attempted in this case. Four of seven patients who suffered cardiac arrest before surgery were resuscitated and operated on successfully. The distribution of the lesions found in the 100 patients is listed in table 1.

TABLE 1.—*Wounds Found in 100 Patients Admitted to Detroit Receiving Hospital*

Location of Wounds	Cases, No.	Deaths, No.
Right ventricle	36	2
Left ventricle	33	3
Right and left ventricles	2	1
Right auricle	8	1
Left auricle	6	3
Left auricle and left ventricle	1	1
Intrapericardial portion of pulmonary artery	1	....
Pericardium only	7	....
Unknown	6	1
Total	100	12

At present, there are some surgeons who prefer to treat penetrating wounds of the myocardium by pericardial aspiration and replacement of blood and to reserve cardiorrhaphy for those patients who do not respond to conservative therapy. The surgeons at Detroit Receiving Hospital favor early surgical exploration and cardiorrhaphy.

Patients suffering from extensive penetrating injuries of the myocardium usually die from hemorrhage before reaching the hospital. They bleed massively into the pleural cavities or even through the cutaneous wound. These patients, if they survive to reach the operating room, present a picture of shock due to blood loss, low systemic arterial pressure, moist clammy skin, and a weak thready pulse. If the situation is not irreversible, these patients respond to blood replacement and to immediate surgical correction of the defects made by the bullet or laceration.

A great many wounds of the heart bleed not into the pleural space but rather into the pericardial sac. This results in tamponade. Since the pericardial sac is relatively inelastic, blood forced into it will create a pressure which interferes with the blood flow from the venae cavae and pulmonary veins into the auricles. This results in an increased venous pressure in both the systemic and pulmonary circulations. As soon as the pressure in the great veins cannot overcome the intrapericardial pressure, circulatory arrest follows. As the stroke volume is reduced, there is a reduction in cardiac output, as well as a decreased flow of blood through the coronary vessels and to the brain. The high venous pressure causes a rise in intracranial pressure, which, in combination with arterial hypotension, diminishes cerebral blood flow, and brain damage may occur.[8] Damage to other vital organs by anoxemia is probable. Acute renal failure resulting from unrecognized cardiac tamponade has been reported.[9] The majority of patients in this series (73%) exhibited classic signs of tamponade on arrival in the emergency room. Only 100 to 250 cc. of blood accumulated in the pericardial sac is sufficient to produce a classic picture of pericardial tamponade.[8] In this situation, the effects on the heart and circulation may be out of proportion to the blood loss.

The falling arterial pressure, the rising venous pressure, and the small quiet heart, as classically described by Beck,[10] aid the physician in differentiating cardiac tamponade from hemorrhagic shock and determine the optimum method of treatment. Under the fluoroscope, the heart will appear only moderately enlarged but will have definite diminution in pulsation. On auscultation, the heart sounds are muffled and distant.

Resuscitative management must be quickly initiated in those patients admitted with penetrating wounds of the thorax or upper abdomen in whom a penetrating wound of the heart is suspected. It is known that if a patient survives to reach the hospital within 30 minutes after injury, survival may be expected. These patients then represent a selected group in which prompt diagnosis and surgical intervention may be lifesaving. Previous to the work of Cooper and co-authors [11] it was thought that cardiac tamponade should not be treated by the rapid administration of intravenous fluid, the idea being that any increase in venous pressure might serve only to increase the existing tamponade. Cooper

CLINICAL NOTES

CHRONIC OCCULT ADRENOCORTICAL INSUFFICIENCY

REPORT OF A CASE

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and
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The classic picture of adrenal insufficiency as described by Thomas Addison in 1868 is well recognized.[1] Recently, Haydar and associates[2] have described seven cases of adrenocortical insufficiency with normal basal levels of urinary 17-hydroxycorticoids and only a few of the typical clinical manifestations of this disease. The patient in the case presented here has had various nonspecific manifestations for many years, which in retrospect may well have been due, at least in part, to borderline adrenocortical function and presented ultimately in a state of acute addisonian crisis.

Report of a Case

A 50-year-old childless housewife was admitted to the Bridgeport Hospital on Jan. 30, 1958, because of recurrent spells of vomiting and syncope for one day. One week prior to admission she experienced transient nausea and diarrhea, which was relieved by administration of a mixture of kaolin and pectin suspended with methylcellulose (Kaopectate). Severe vomiting and watery diarrhea recurred two days before admission and persisted to the point of prostration, despite the administration of prochlorperazine (Compazine). On admission via ambulance, there were recurrent, brief syncopal episodes.

Since the age of 18 years the patient had had fainting and weak spells occurring once or twice a month, usually with menstrual periods or in association with illness, pain, or other stress. In the past two years, there were episodes of diarrhea, bronchitis, or pharyngitis on different occasions, and, in each instance, the illness was characterized by a prolonged period of malaise and weakness, with convalescence lasting several weeks. Because of a protein-bound iodine determination of 3.6 mcg.%, therapy with 30 mg. of dessicated thyroid daily was instituted but produced no significant change. Since the second decade of her life, the patient has had areas of vitiligo on her neck, upper trunk, and arms. These patches gradually increased in size and became both more extensive and prominent, very much so in the past two years. The surrounding areas of skin were noted to darken in contrast. Because of this problem, the patient deliberately avoided sunbathing, nor did she wear garments which would not cover her neck and arms.

In May, 1957, the patient was admitted to St. Vincent's Hospital for generalized convulsive seizures, which had been preceded by several days of vomiting and diarrhea. Two prior "fainting spells," each lasting 10 minutes, were described; several successive episodes occurred in bed. In the course of her narration, she suddenly complained of epigastric distress and announced that she was going to faint. There was sudden stiffening of both arms and legs, tightening of the jaw, with eyes rolling upward in the orbits. The heart beat remained slow and regular, and there was no urinary or fecal incontinence. After 10 minutes of relaxed unconsciousness, the patient recovered in a drowsy state, without full recall of the episode. The only laboratory abnormality noted during this brief hospitalization was diffuse cortical irritability demonstrated on the electroencephalogram. Diphenylhydantoin (Dilantin) sodium was prescribed, with continued effect while administered. Except for chronic fatigue and somewhat debilitating upper respiratory infections, the patient was thereafter reasonably well until her present admission.

The medical history included poliomyelitis in childhood, with slight residual weakness of the left arm, and urticaria from sulfonamides. The surgical history included tonsillectomy; appendectomy in 1941, complicated by pulmonary embolism; and cholecystectomy with prophylactic bilateral femoral-vein ligations in 1947. Varicose-vein surgery on the right leg had been performed on two subsequent occasions.

On the patient's admission, physical examination revealed a blood pressure of 130/88 mm. Hg, a temperature of 98.4 F (36.89 C), pulse rate 124 per minute, and respirations 20 per minute. The patient was a well-developed and well-nourished woman appearing acutely ill, dehydrated, and prostrate. Prominent, 5 to 10 cm. vitiliginous areas were present on the neck, shoulders, chest, arms, and on the dorsum of the right hand. Minimal pigmentation

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right atrial pressures will maintain cardiac filling, even with moderate increases in airway pressure. This seems to be advantageous in patients suffering from cardiac tamponade.

This is in direct contrast to persons anesthetized with a rapid-acting barbiturate. Here vasomotor responses are not well maintained in persons subjected to raised airway pressure.[16] Thiamylal sodium was used as an induction agent in a few patients in this series who were not in severe shock. One of these patients died after a slow injection of 350 mg. of thiamylal sodium. No conclusion about the actual cause of death in this case can be drawn, since the anesthetist persisted in his efforts to intubate the trachea rather than oxygenate the patient with a mask and rebreathing bag.

The use of cyclopropane in heart surgery has been criticized because serious disorders of cardiac rhythm may arise during its use or result after its use. That we have encountered no difficulty is probably due to the extremely light plane of anesthesia that is maintained during the course of surgery and because every effort is made to maintain adequate ventilation by assisted or controlled respiration. Arrhythmias, particularly ventricular ectopic beats, are noted frequently during the course of surgery.

TABLE 3.—*Complications Occurring After Cardiorrhaphy*

Complication	Patients, No.
Myocardial damage, nonspecific, revealed by EKG	28
Myocardial infarction	5
Right or left bundle-branch block	6
Pericarditis	10
Pleural effusion	3
Cardiac enlargement	1
Empyema	1
Chondritis	1
Total	55

These arrhythmias are related to manipulation of the heart by the surgical team and cease spontaneously when manipulation ends.

Ether also may cause arrhythmias, which are usually of auricular origin. Because of its vasodilator effects, it is generally not a good agent for patients in shock. Ether analgesia can be used safely, although it may require deep anesthesia at the beginning, and it is time-consuming. For these reasons, it was not used in this clinic. Nitrous oxide administered with sufficient oxygen has no toxic properties, but unfortunately it is an impotent agent. In combination with succinyldicholine, nitrous oxide in 50% concentration with oxygen provided adequate analgesia for a few patients in this series. For patients who arrive in an operating theater sustained only with an infusion of norepinephrine, this combination may be useful. The four patients who received oxygen only were moribund on their arrival in the operating theater and could not be resuscitated.

The average length of hospitalization for this group of patients was 14 days. Coexisting injuries prolonged their stay in some instances. Postoperative complications are not uncommon in patients suffering from trauma to the heart. No serious complications referable to anesthesia were seen in this group of patients. The most common complications are listed in table 3.

Summary

Cyclopropane was the preferred anesthetic agent for thoracotomy and cardiorrhaphy in 94 patients suffering from penetrating wounds of the heart. One hundred cases of penetrating injury to the myocardium are reported; 12 patients died, for an over-all mortality of 12%.

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might be expected, steroid therapy reduced the intensity and extent of hyperpigmented areas and seemed to cause regression of the depigmented areas as well. It could be postulated that her adrenocortical function was marginal and thus almost adequate for daily routine but, under stress, inadequate to suppress pituitary secretion of melanin-stimulating hormone.

This patient had episodes of syncope and seizures intermittently (also over the 20-year period), which she accepted as fainting spells. These, too, were associated with dysmenorrhea, diarrhea, or other illness. At no time was she detectably hypoglycemic, but her electroencephalogram revealed diffuse increased irritability. She had no further seizures after temporary institution of diphenylhydantoin sodium therapy, or later when given steroids alone. Brain wave abnormality and seizures are less common manifestations of adrenal cortical hypofunction (Addison's disease) but are known to occur.

In retrospect, gradually increasing lassitude over a few years is apparent. Our patient voluntarily restricted her community and social activities because she found them too tiring. As noted in her history, at times of minor illness, she confined herself generally to a reclining chair or bed. This manifestation led to the previous erroneous impression of mild hypothyroidism, which did not respond to therapy with thyroid extract.

It is now evident that her gastrointestinal symptoms, including frequent bouts of indigestion, nausea, and occasional episodes of vomiting and diarrhea were reflections of her adrenocortical insufficiency.

Summary

In a patient with chronic adrenal insufficiency the less common characteristics observed were paucity of symptoms under favorable conditions, recurrent symptoms under varied stress, normal basal levels of 17-hydroxycorticosteroids, and lack of significant adrenal response to administration of ACTH.

It is suggested that the syndrome of relative adrenal cortical insufficiency may be more common than has been realized heretofore.

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The urinary 17-hydroxycorticosteroid levels were determined by Dr. S. P. Gottfried, Chief Biochemist, Bridgeport Hospital, according to the method of Reddy.

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THE "TOURNIQUET-SHOCK SYNDROME" IN LOWER LIMB GANGRENE OF VENOUS ORIGIN

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The comparative rarity of gangrene of venous origin prevents widespread recognition of the subtle nature of this insidious disease. The full-blown clinical picture is a dramatic one that has been described with increasing frequency in recent years.[1]

The case described below demonstrates a rare, fatal variation in which the sudden, complete, thrombotic closure of all the venous channels of an extremity resulted in the trapping of much of the circulating blood volume of the patient in the affected limb. Despite energetic measures, the resulting shock syndrome led to the patient's death.

Report of A Case

A 69-year-old man was admitted to the medical service of the Mount Sinai Hospital on Dec. 17, 1957, with a complaint of increasing pain and swelling of the right leg of two weeks duration. He was known to be a diabetic who had been under treatment for one year and had been seen last two weeks prior to admission because of pain in one leg, which was not swollen at that time.

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was noted in the palmar creases and in the abdominal operative incision scar. Her tongue was dry; the neck was supple. The thorax, breast, and lungs were unremarkable. The heart revealed sinus rhythm, rate of 100 per minute, without enlargement or murmurs. The extremities were slightly flaccid, without abnormal reflexes.

Roentgenograms of the chest and abdomen were normal. The electrocardiogram showed sinus tachycardia. The initial blood cell count revealed a hemoglobin level of 18.7 Gm.%, hematocrit reading 57%, and a normal white blood cell count and differential count. The blood urea nitrogen level was 8.8 mg.% and the fasting blood sugar level 112 mg.%. Therapy was started promptly with 1,500 cc. of 5% glucose in saline solution intravenously, and intramuscularly given prochlorperazine (Compazine), 10 mg. three times daily. Serum electrolyte values on the next day revealed a carbon dioxide content of 9.5 mEq. per liter and sodium content of 135 mEq. per liter. Phosphorous and calcium levels were 5.2 mg.% and 9.1 mg.% respectively. The patient was given an intravenous infusion of 1,500 cc. of 5% dextrose in saline solution with 100 mg. of hydrocortisone. The total eosinophil count of 286 per cubic millimeter fell to only 220 per cubic millimeter four hours after intramuscular administration of 25 units of ACTH-gel. On Feb. 3, 1958, the 24-hour urinary 17-hydroxycorticoid level was 1.4 mg.[3] After three days of daily stimulation with 100 units of ACTH-gel, the 24-hour urinary 17-hydroxycorticoid level rose to only 3.7 mg. At the same time, while on an unrestricted salt diet, the patient's 24-hour urinary sodium-chloride output was determined to be 8.9 Gm. During this period there was gradual clinical improvement, with prompt subsidence of nausea, vomiting, diarrhea, and weakness. Hydration, strength, hemoconcentration, acidosis, and the electrolyte picture improved. The vitiliginous areas seemed somewhat less prominent. The patient was discharged on Feb. 8, 1958, to be followed up as an outpatient.

Since her discharge, the patient's over-all progress has been gratifying. Because of her initial gastrointestinal intolerance to orally given hydrocortisone and dread of injections, desoxycorticosterone (Doca) acetate 5 mg. linguets twice daily were substituted. The hyperpigmented areas seemed to fade in some places and in others to regress in extent. The patient gradually felt more like performing her usual domestic and social functions and, under supervision, was able to reduce her medication to 5 mg. of desoxycorticosterone acetate daily, increasing it to 10 mg. in times of stress. This improvement continued until the time of her last visit, which was 14 months after the institution of this regimen. The patient stated that she felt stronger and enjoyed greater well-being than she had in years.

Comment

Recently a syndrome of relative adrenal insufficiency, appearing during periods of stress has been well documented.[2] This manifests itself as an inability on the part of the patient to ward off minor illness. The case presented recounts a long history of syncope, vomiting, diarrhea, prostration, upper respiratory infections, hyperpigmentation, convulsions, and generally poor response to stress. The suggestion of relative adrenal insufficiency is confirmed by a lack of significant steroid response after ACTH administration. The diagnosis was reaffirmed by the gratifying response to treatment.

The long history and the difficulty in establishing the diagnosis are not in themselves unusual. Certain aspects of this disease pattern, such as vitiligo and convulsions, bear close inspection, as representative of the less common manifestations of adrenal insufficiency.[1] In our particular case, the basal urinary 17-hydroxycorticosteroid levels were in the low normal range for our laboratory. The only diagnostic test was the failure of the urinary 17-hydroxycorticosteroid level, to rise after ample stimulation by ACTH. The lack of a fall in the eosinophil count was suggestive but not confirmatory. As is so frequently the case, the serum electrolyte and blood sugar values and the blood pressure were within normal limits.

Haydar and associates [2] described a series of seven similar cases of partial adrenocortical insufficiency. Abnormal pigmentation and weakness were present in most patients, but weight loss, hypoglycemia, electrolyte imbalance, and hypotension were not prominent features. Two patients had abnormal electroencephalograms showing varying nonspecific patterns. Their patients also became symptomatic under stress.

Our patient complained only of long-standing and increasing vitiligo or prominence in the appearance of her vitiligo. This manifestation had been present for over 20 years but, in the past few years, had been so prominent that she was forced to modify her dress and activity. The brownish areas of hyperpigmentation surrounding the light patches would become increasingly dark during the time of a mild upper respiratory infection, the menses, or gastrointestinal upsets. Noradrenaline and adrenaline are both produced at the adrenergic nerve endings and in the adrenal medulla.[4] These substances antagonize the action of the melanin-stimulating hormone on the melanocytes in the skin. When these pressor substances appear in excess in these areas, vitiligo is thought to occur. On the other hand, as a response to adrenal hypofunction, the pituitary releases increased melanin-stimulating hormone. This in turn is responsible for the hyperpigmentation.[5] Thus, two antagonistic mechanisms occurred simultaneously in different areas. As and that the patient was losing blood into the vasculature and tissue spaces of the extremity at a dangerous rate. At this time, the circumference of the thigh was 46 cm. and that of the leg, 36 cm. The comparable dimensions of the unaffected left limb were 34 cm. and 25 cm. respectively (see figure). More blood was administered, 200 mg. of vitamin K_1 phytonadion, (Mephyton) was given, and a tight tourniquet was placed just above the knee in a gangrenous area to lessen the arterial inflow into the right leg. At 7 p.m., four hours later, the blood pressure was elevated to 100/80 mm. Hg as a result of repeated transfusion, but the circumference of the thigh had now reached 50.5 cm. and that of the leg, 36 cm. From the changing dimensions and computations set forth in the table, it was evident that a large amount of blood was still being lost into the extremity. Accordingly, a strongly pulsating right common femoral artery was divided between suture-ligatures of linen thread, with the patient under local anesthesia. The femoral vein was solidly thrombosed.

After this procedure the blood pressure and pulse became stabilized. However, glycosuria and acidosis persisted. The patient appeared toxic, which indicated the need for amputation. The operation was performed on the eighth day after admission of the patient, the level of section running through the line of demarcation, 3 in. below the inguinal ligament. All the tissues were suffused with a dark red fluid, all veins were thrombosed, and the only bleeding was arterial.

After the amputation the patient continued to do badly. His acidosis was not controlled and there was increasing difficulty with the fluid and electrolyte balance. Some electrocardiographic changes occurred, which were thought not to be due to infarction. Three days after the amputation and 10 days after admission, the patient suddenly died. The apparent cause was pulmonary embolism. Permission for autopsy was refused.

Comment

The term "tourniquet-shock syndrome" is applied to that experimentally induced state in which tourniquets were placed about an animal's extremities in such fashion as to prevent the return of venous blood and so trap a great part of the circulating blood volume in the engorged limbs. A state of shock is produced which leads to progressive ischemia of the vital viscera and death. This is essentially what took place in this patient.

At noon on the fifth day, when the signs of shock first manifested themselves, the patient's right lower extremity was twice the size of the left, or 5 liters larger (see table). The patient apparently was able to accommodate to this loss, since it took place over a period of four days. However, as the morbid pace increased and over one liter was lost within the next four hours and an additional 2 liters before the interruption of the right femoral artery, the lethal nature of the process became evident. Once the arterial inflow was stopped, it was possible to transfuse enough blood to restore the systemic, circulating blood volume.

Emphasis on the rate of venous occlusion in this condition has been made by Veal.[2] The essential point, as demonstrated by the case here presented, is the variability and unpredictability of this dangerous condition.

Summary

In a case of gangrene of venous origin in the right lower limb, severe shock resulted from entrapment of a large amount of blood in the engorged limb. This was caused by sudden, massive, thrombotic occlusion of all the venous channels.

Estimated Volumes of Limbs of Patient with Gangrene, on Fifth Hospital Day*

	Time	Circumference, Cm.	Estimated Vol., Cu. Cm. as Cylinder†	Estimated Vol., Cu. Cm. as Frustum of Cone‡
Left thigh	..	34	3,464.4	3,679.2
Left leg	..	25	1,672.3	1,716.8
Total			5,136.7	5,396.0
Right thigh	3 p.m.	46	6,696.8	6,715.8
Right leg	3 p.m.	36	3,605.0	3,622.3
Total			10,301.8	10,338.1
Right thigh	7 p.m.	50.5	8,080.0	7,639.8
Right leg	7 p.m.	36	3,605.0	3,622.3
Total			11,685.0	11,262.1
Right thigh	9 p.m.	53	8,920.0	8,950.2
Right leg	9 p.m.	37	3,815.0	3,848.0
Total			12,735.0	12,798.2
Right thigh	10 p.m.	54	9,240.0	9,290.4
Right leg	10 p.m.	37	3,815.0	3,855.4
Total			13,055.0	13,145.8

* Length of thighs, 40 cm.; length of legs, 35 cm.

† $V = \pi r^2 h$; r = radius; h = height.

‡ $V = \frac{1}{3}\pi h(R^2 + r^2 + Rr)$; r = small radius; R = large radius.

It should be emphasized that this serious complication can occur in any case of thrombophlebitis, particularly when an evident increase in swelling and cyanosis occurs.

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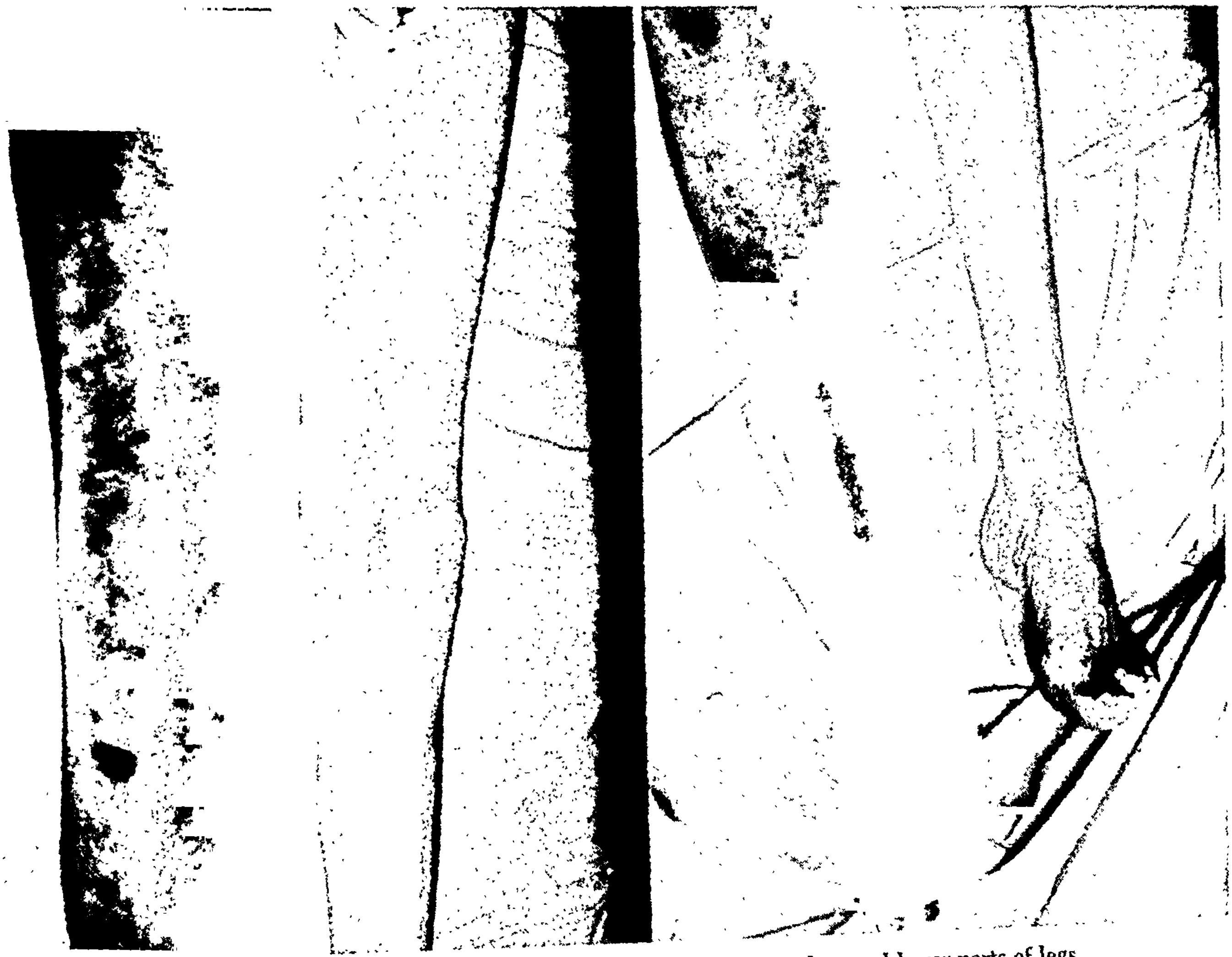
During the previous few months, he had also received medicaments for bilateral intermittent claudication. The recent pain, however, was quite different in that it was persistent, remained in the medial part of the thigh and the leg, and was confined to the right lower extremity.

On examination, the vital signs were normal, with a pulse rate of 88 per minute, a respiration rate of 18 per minute, and a temperature of 98.8 F (37.1 C). The blood pressure was 135/75 mm. Hg. The patient seemed older than his years, pale, emaciated, and chronically ill; he was intelligent and cooperative. The pupillary reflexes were sluggish, and, because of early cataract formation, the eyegrounds were barely visible. There was arterial narrowing, with pale, cupped disks. The pharynx and neck were normal, the chest clear, and the heart clinically normal. Findings of the remainder of the examination were essentially normal, except for the absence of oscillations and pulses below the knees and a marked edema of the right leg. The toes of the right foot were slightly cyanotic but warm.

The admission diagnosis was diabetes mellitus, arteriosclerosis obliterans, right iliofemoral thrombophlebitis, bilateral cataracts with chronic, simple glaucoma, and possible neoplastic disease. In addition to the usual battery of laboratory tests, the patient was started on an anticoagulation regimen with bishydroxycoumarin (Dicumarol).

After 48 hours, because of persistence of pain in the extremity, a paravertebral block was performed, without apparent benefit. By the third day, the toes of the right foot were deeply cyanotic and the possibility of gangrene of venous origin due to spread of the phlebitic process was considered. The pain was more severe, but the general condition was unchanged. The prothrombin time (Quick method) was 41 seconds. Another paravertebral block with 1% lidocaine (Xylocaine) hydrochloride resulted in some lessening of pain. On the fifth day, together with an increase in the pain and size of the right lower extremity, the discoloration extended up into the thigh, the pulse rate rose progressively, and the blood pressure dropped to 70/58 mm. Hg. A transfusion was begun and a surgical consultation requested.



Left, gangrenous and normal thighs and, *right*, gangrenous and normal lower parts of legs.

When seen by us at 3 p.m., the patient was in obvious shock. The right thigh and leg were tensely swollen and cyanotic. The right femoral pulse was easily palpable. It was evident that a complete block of the venous outflow had occurred and disappearance of the mass previously occupying the distal end of the esophagus (fig. 2*B* and 2*C*). There was a residual mild degree of achalasia present. The patient noted complete relief of pain about six hours after the roentgenograms were taken on Sept. 25, 1959.

The patient has done well, to the time of writing, on a diet of soft and puréed foods. She has gained weight and has no complaints referable to the esophagus.

Comment

The most common foreign bodies found in the esophagus are impactions of foods that are normally ingested. Meat, especially pork, is the commonest food,[1] although persimmon skins,[2] celery, and shredded coconut may also become impacted. The patients are usually elderly and often have poor dentures.[3] Hygroscopic bulk laxatives such as Serutan[4] and karaya gum[5] may become impacted in the lower end of the esophagus, by virtue of imbibition of fluid in the esophagus.

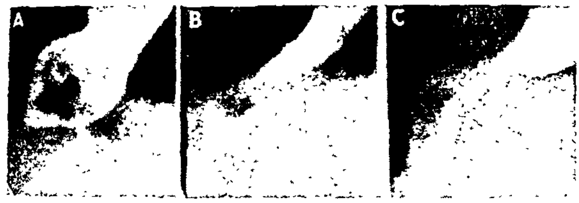


Fig. 2.—Spot films of fundoesophageal region, disclosing alteration in contour and outline of inspissated congealed food particles. *A*, beginning disintegration noted after 12 hours of medical therapy (Sept. 25); *B*, complete disintegration and disappearance of bolus of congealed food which formerly occupied distal end of esophagus. Mild degree of achalasia persists (Sept. 28); *C*, residual achalasia, mild in degree, with no evidence of pathological alteration of internal architecture of fundoesophageal junction (Oct. 14).

Richardson[3] first reported the satisfactory digestion of boli of meat with the use of papain, a proteolytic enzyme which converts protein to amino acids. This has been confirmed by Schaff and McCallen,[6] who recommended that the patient drink 1 to 4 ml. of a 5% solution of papain (caroid) every 15 minutes. In this way, they found that the esophagus could be cleared in 90 minutes or less.

Johnson[4] used the starch digestant Taka-diastase to remove an impacted bolus of Serutan. Miller and Godfrey[7] treated a patient with a large bolus of cooked meat impacted in the esophagus by instillation of crystalline trypsin. This patient had undergone transesophagoscopic removal of part of the contents, but the operation had to be terminated because of the patient's condition. Incidentally, these authors did not use papain because they found that a suspension of the enzyme contained a gram-positive micrococcus.

Our patient had a mild achalasia of the esophagus and poor dentures. She swallowed a large bolus of fish roe, probably with a minimal amount of chewing. Preparatory to attempting removal via the esophagoscope in an emaciated patient, it was decided to try enzymatic digestion. Because of the nature of the bolus, it was felt that a combined enzyme powder would give a broader spectrum of digestion than any individual enzyme. Checking the diagnosis with roentgenography and a "barium swallow" did not seem to impede the dissolution of the bolus to a significant extent.

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THE SCIENTIFIC CONCEPT OF DISEASE.—The traditional attitude toward disease tends in practice to restrict what is categorized as disease to what can be understood or recognized by the physician and/or what he notes can be helped by his intervention. This attitude has plagued medicine throughout its history and still stands in the way of the physician's full appreciation of disease as a natural phenomenon. Disease cannot be defined on the basis of the function of physicians, which is a social and institutional phenomenon. The scientific attitude requires that a clear distinction be made between the study and understanding of disease as a natural phenomenon and the categorization of disease in terms of the function and role of the physician in a society. Only the first is relevant to a scientific concept of disease. The latter changes with time and circumstance.—G. L. Engel, M.D., A Unified Concept of Health and Disease, *IRE Transactions on Medical Electronics*, January, 1960.

IMPACTION OF FOOD BOLUS IN THE ESOPHAGUS

Louis Pelner, M.D.
and
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An aged patient in poor general health had an impaction of the lower end of the esophagus after eating fish roe. It was decided to attempt to digest the foreign body by enzymatic means.

Report of a Case

A 76-year-old woman, who appeared older than her stated age, complained that for a week she had had severe pressure in the retrosternal area. This pressure made her gasp for breath, but the symptom was not made worse by walking. She stated that she continually "brought up phlegm," but it could not be ascertained whether the material was vomited or expectorated. She also complained of weakness.

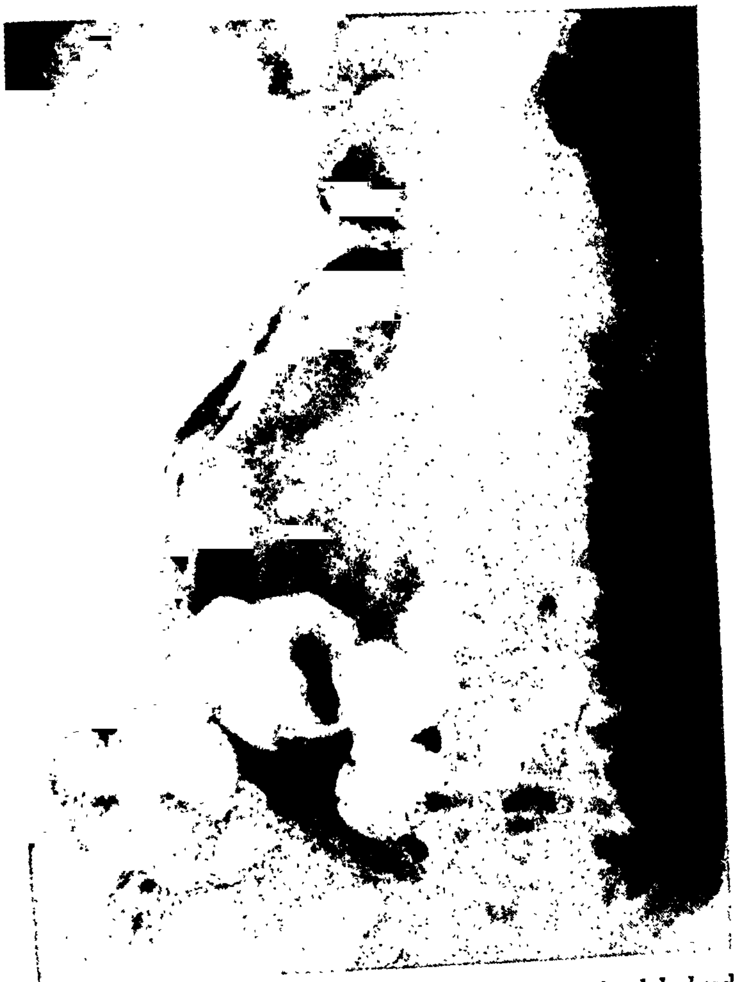

Fig. 1.—Tangerine-sized congealed bolus of food lodged in lower end of esophagus, with some associated achalasia (Sept. 24, 1959).

There was evidence of considerable weight loss. The patient had poorly fitted dental plates. The heart was slightly enlarged, and a presystolic murmur was heard at the apex and base. An electrocardiogram showed a few nonspecific changes. The blood pressure was 160/90 mm. Hg, the lungs were clear, and there was no enlargement of the liver or edema of the legs or other sign of heart failure.

The patient had recently undergone cataract surgery. The ophthalmologist had postponed the operation several times because the patient appeared to be in poor condition, although the examination each time failed to reveal any definite contraindication to operation. She appeared to lack the stamina to sustain the rigors of an operation successfully.

Since there were insufficient findings to warrant consideration of the heart as the source of her symptoms, an esophagram was made on Sept. 24, 1959. The esophagram revealed "a pleomorphic, tangerine-sized area of radiolucency occupying the lower end of the esophagus at the fundoesophageal junction. The somewhat circular contour of the filling defect seems to point to one of three possibilities, i. e., (1) an intramural leiomyoma, (2) an undescended, large congealed bolus of food, and (3) the possibility of a large . . . polyp. In addition, it was noted that cardiospasm was present, with some dilatation of the barium-filled esophagus" (fig. 1). Other physiological findings included a moderate degree of hypertrophic osteoarthritic lipping of the cervical and dorsal spine, a slightly enlarged heart, with calcification of the mitral ring, and moderate hilar vascular engorgement.

On close questioning, the patient recalled that all her symptoms had started after she had swallowed a large mouthful of fish roe. Thereafter she felt a severe pressure behind her sternum and vomited all her food.

Before subjecting this weak, emaciated patient to esophagoscopy, it was thought that enzymatic digestion should be given a short trial. It was necessary to find an enzyme preparation that could digest protein, carbohydrate, and perhaps some fat. An enzyme powder containing 200 mg. of pepsin, 100 mg. of pancreatin, and 100 mg. of diastase per gram (Peptenzyme), ½ teaspoonful in ½ glass of water, was prescribed to be sipped slowly and repeated every two hours. After three doses of this enzyme preparation there was a definite alteration of the contour and outline of the mass, which showed beginning disintegration (fig. 2A). The enzymes were therefore given at two-hour intervals. Further films showed complete disintegration

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associated with one of two processes in women, either defeminization or frank virilization. The defeminizing group of symptoms includes a loss of feminine contours, slight decrease in the size of the breasts and genitalia, a recession of frontal hair in the pattern of early male baldness, amenorrhea, acne, and coarseness of the skin. The virilizing symptoms include the aforementioned symptoms plus hirsutism of a coarser, heavier, male type, as well as male-pattern alopecia, a deeper voice (and enlarged "Adam's apple"), muscular development, significant atrophy of the breasts and genitalia (with amenorrhea), and an enlarged clitoris.

TABLE 2.—*Hirsutism by Degree of Associated Endocrine Change, Type, Origin, and Underlying Disorder*

	No Detectable Endocrine Change or Minor One with Hirsutism			
	Idiopathic	Physiological	Therapeutic	Miscellaneous
Origin	Racial Familial Androgen-sensitive	Puberty Pregnancy Menopause	Especially androgenic and other steroid hormones administered	Congenital Familial Trauma Local irritation Others*
	Major Endocrine Changes Associated with Hirsutism			
	Adrenal	Ovary	Pituitary	
Symptoms and Underlying Disorders	With virilization Adrenogenital syndrome Without virilization Adrenal cortical hyperfunction (Cushing's syndrome) (Mixture of Cushing's syndrome and adrenogenital syndrome not uncommon)	Stein-Leventhal syndrome	Without virilization Pituitary basophilism (Cushing's disease) Acromegaly Achard-Thiers syndrome Adiposogenital dystrophy	
	Miscellaneous and Borderline Endocrine Types			
Underlying Disorders	(?) Metabolic craniopathies and others (especially hypothalamic tumors resulting in excessive secretion of pituitary gonadotropin)			

* Uncommon, obscure causes of hirsutism include congenital ectodermal dysplasia, mumps, encephalitis, various neuritides, multiple sclerosis, and porphyria.

An inclusive grouping of present-day concepts of hirsutism is presented in table 2, with an approximate listing in the order of frequency.

Types, Origin, and Treatment of Hirsutism

According to Ferriman and associates,[6] major grades of hirsutism are found in 10 to 15% of unselected patients admitted to a hospital. The hair growth in these patients may be localized or widely distributed. It usually begins during adolescent periods of changing endocrine activity and progresses to some predetermined limit. In their studes, 17-ketosteroid and fraction levels were unrelated to patterns of hair distribution, although higher levels were generally associated with coarser hair, denser growth of hair, and larger areas of nvolvement in these patients.

The largest group of people with hirsutism are either those with no detectable endocrine changes or those in whom the endocrine changes are mild n degree, often transitory, and on a physiological basis or possibly produced by hormone therapy.

Idiopathic Hirsutism.—Idiopathic hirsutism is probably the commonest grouping of hirsutism in women. The tendency toward this type of hirsutism may be familial and often appears in women of Mediterranean origin. The growth of facial hair in these women may be extremely abundant. The hair pattern on the chest, linea alba, and extremities may be practically masculine. Although investigative studies done in former years disclosed no specific metabolic, chemical, or endocrine changes in this disorder (thereby accounting for the name idiopathic or constitutional hirsutism), recent investigations, with vastly refined biochemical techniques, developed facts to the contrary. As a result of these studies, it has become possible to considerably diminish the degree of hirsutism—a major breakthrough in this hitherto mysterious disorder. The sequence of events leading up to this discovery may be summarized by going back to the year 1937, when Kenyon and his colleagues,[7] as well as other investigators, were unable to demonstrate a definite increase in urinary androgens in patients with idiopathic hirsutism. The next year, however, Callow[8] observed that several women with this condition excreted moderately elevated quantities of urinary 17-ketosteroids, a finding that has since been confirmed by other workers. The idea that cortisone might be effective in the treatment of hirsutism was first suggested in 1948 by Whitaker and Baker,[9] who found that cortisone had an inhibitory effect on hair growth in rats. In 1950 and 1951, Wilkins and co-workers[10] showed that the administration of cortisone to patients with congenital adrenal hyperplasia caused moderately decreased excretion of 17-ketosteroids and biologically active androgens, as well as an unquestioned decrease of hirsutism. In 1953, Jones, Howard, and Langford[11] extended the work of Wilkins and discovered that cortisone therapy resulted in a diminution of urinary 17-ketosteroids in certain women with idiopathic hirsutism. Gardner[12] also found abnormally high 17-ketosteroid and dehydroepiandrosterone excretion in similar patients who responded to cortisone therapy, with a decrease in steroid excretions to normal values.

COMMITTEE ON COSMETICS

Report to the Committee

The Committee on Cosmetics has authorized publication of the following report.

Veronica L. Conley, Ph.D., *Secretary.*

DIAGNOSIS AND MANAGEMENT OF HIRSUTISM

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Hirsutism or hypertrichosis is a term used to indicate the presence of excessive hair on various body surfaces which normally grow hair or the appearance of hair on body regions which are normally hairless. The term is somewhat relative in that what might be considered excessive and unwanted depends upon the individual, the sex, and even the race. For example, a mustache is preferred by some men and unwanted by most women; yet, a light growth on the upper lip of women is considered a sign of a loving nature in certain Latin countries and therefore is desirable to a woman. Axillary hair is hastily shaved, depilated, or removed in some manner by most American women but is carefully preserved by women in many other countries. A full head of hair is a much desired masculine attribute; yet, one well-known male screen star has made tremendous capital of his shining bald pate. These examples illustrate the great variability in the personal concept of the term "hirsutism," inasmuch as it is often a matter of individual, sexual, and group attitudes, styles, and beliefs. From a medical standpoint, however, we are basically concerned with this problem when the hirsutism deviates sufficiently from the norm to concern the person or when it is indicative of some underlying disorder. Although a slight degree of hypertrichosis is not unusual and is rarely associated with systemic disease or glandular aberration, unusual amounts and abnormal localizations of hair growth merit comprehensive medical and endocrinologic study in order to rule out the possibility of some underlying disorder. It should be emphasized that any sudden change in the quantity or distribution of hair, except during puberty, pregnancy, and the menopause, is of far greater significance than the slow and gradual appearance of hirsutism and should be thoroughly investigated.

Classification

The classification of human hair as originally proposed by Danforth[1] and Garn[2] was modified by Flesch.[3] He classified human hair from the point of view of endocrine influence as follows:

1. Hair that is the same in both sexes and is not primarily under hormonal control. This includes lanugo hair all over the body, eyebrows, eyelashes, and probably some of the hair on the extremities.
2. Ambosexual hair under endocrine control. This include the coarse hair that is present after puberty to the sam extent in normal representatives of both sexes. Ambosexua hair is represented by axillary hair and a major (mostly th lower) portion of the pubic hair; scalp hair may also b discussed in this category.
3. Hair that serves as a true secondary male characte Terminal hair on the face, beard and mustache, are th main representatives of hair which is present in all sexuall mature and normal males but not in females. In most mal varying amounts of upper pubic hair on and around t linea alba also belong to this group, as well as hair in t external ear canal, a distinct male characteristic. Finall the larger amounts of body hair, like hair on the che shoulders, abdomen, and back of hairy men, are also sex characteristics.

As will be discussed later, the variable degre and types of hirsutism depend primarily on t quality and quantity of hormonal stimulation a the responsiveness of the hair follicles in the affected area. There have been numerous attempts to classify hirsutism and its causative mechanisms. Greenblatt[4] suggested the groupings as seen in table 1.

Table 1.—*Classification of Hirsutism by Its Contributing Conditions*

Glandular or Genetic Area of Influence			
Pituitary	Adrenal	Ovary	Genetic
Pituitary basophilism (Cushing's disease)	Tumor Adrenogenital syndrome Adrenal cortical hyperfunction (Cushing's syndrome)	Tumor Arrhenoblastoma Adrenal rest tumor (hypernephroma)	Racial or familial tendency Sensitivity to intrinsic androgens
Achard-Thiers syndrome (?)			
Acromegaly	Hyperplasia Congenital pseudohermaphroditism	Ovotestis Hermaphroditism	
Syndrome of excess luteinizing hormone (?)	Postnatal adrenogenitalism	Stein-Leventhal syndrome	
Porphyria			

De Alvarez and Heitman[5] tentatively grouped hirsutism in women into three major categories: (1) in association with a virilizing endocrinopathy, (2) in association with a nonvirilizing endocrine disorder, and (3) with no recognizable endocrine disorder. Hirsutism of endocrine origin is often

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Physiological Hirsutism.—Physiological hirsutism applies to the excessive growth of hair during the periods of puberty, pregnancy, and the menopause. The causative mechanisms are probably adrenocortical in origin, although gonadal and pituitary factors also play a role. In addition, the slight degree of hirsutism occasionally observed during pregnancy may be due to placental secretion of androgens, adrenocorticotropins (ACTH), and gonadotropins. This mild hirsutism is temporary, whereas the others are permanent. During the menopause, the hairs become thicker and darker on the upper lip and chin especially, as well as on the facial margins and the pubis. Mazer and Israel[17] refute the hypothesis that hirsutism in women is merely due to estrogen shortage, by citing instances of women with primary hypogonadism who have little or no estrogen and do not have hypertrichosis. They state that hirsutism in women is due to excessive androgen production by the adrenal cortex, as evidenced by (1) the greater urinary excretion of androgens by hirsute women and by those with adrenocortical tumors and (2) the ability of androgens (when given in large doses) to produce hirsutism in female patients of any age.

Therapeutic Hirsutism.—Testicular androgens are responsible for the growth of the mustache and beard, as well as for the development of coarse hair on the trunk and extremities of a man. They are also essential for the development of adult axillary and pubic hair patterns. The administration of testicular hormones to women, in sufficient dosage and for a long enough period, will result in hirsutism of the upper lip and, eventually, of the chin and cheeks. The majority will show distinct effects after an approximate total dosage of 500 mg. of testosterone propionate or 1.2 Gm. of methyltestosterone. Other effects include acne, enlargement of the clitoris, and vocal changes. Male-patterned alopecia and body hirsutism do not occur unless large amounts are administered over long periods of time. Similar effects have been observed after the administration of large amounts of cortisone and adrenocorticotropin.

Miscellaneous Causes of Hirsutism.—This smaller grouping of hypertrichotic patients includes congenital or acquired cases, as well as general or partial examples of excessive hair growth. The congenital types (excluding those with endocrinopathy) are rare. A dense, silky hair coat somewhat like the coat of an Angora animal may cover the body in such cases. Other developmental defects may be present. Partial congenital hypertrichosis is not unusual; it may be associated with nevi such as the bathing trunk type of nevus pilosus. Partial acquired hypertrichosis (unrelated to endocrinopathy) may occur at sites of constant local irritation. It is observed on skin areas under plaster casts and as a result of constant irritation or friction with liniments, plasters, rubefacients, and similar agents. Other uncommon and obscure causes of hirsutism include congenital ectodermal dysplasia, mumps, encephalitis, certain types of neuritis, and multiple sclerosis.

Hirsutism of Adrenal Origin.—Major endocrine changes of adrenal origin may result in the development of two syndromes characterized by hirsutism. Mixtures of both syndromes often occur, depending on the type of hormones secreted. If the hyperactive adrenal cortex produces testosterone-like hormones, the resultant picture is that of the adrenogenital syndrome. If the excessive hormones are hydrocortisone and derivatives, the result is a clinical picture often called Cushing's syndrome.

Adrenogenital syndrome is characterized by virilizing symptoms and may be due to either a hyperplasia or tumor of the adrenal cortex. Depending on the time of its occurrence (fetal, childhood, or adult life) and the sex of the patient, the symptomatology is variable. If it is of fetal origin, the female child is often a pseudohermaphrodite, with an enlarged clitoris and persistent urogenital sinus. With precocious growth and development, the female infant later develops heterosexual features similar to those occurring in the childhood and adult cases; namely, (1) body and facial hirsutism, increased strength, and muscular development, (2) a lowering of the vocal range from soprano to tenor, (3) an enlarged clitoris, (4) advanced bone age, (5) amenorrhea, (6) absent or atrophic breasts, and (7) male-pattern baldness. This obvious virilization or masculinization is often associated with elevated urinary neutral ketosteroids. The 11-hydroxycorticoids are usually normal. Treatment of these patients is entirely dependent on the type of syndrome present. If a tumor is present, surgical extirpation will often cure the disease. If the adrenal process is merely a hyperplastic one, steroid hormone therapy plus adequate physiological and chemical measures, depending on the individual case, are essential.

So-called Cushing's syndrome, a disorder of the adrenal gland, is due to an increased secretion of hydrocortisone and its derivatives (panhypercorticalism). It is not common and is found primarily among women in the third or fourth decade of life. It is characterized by weakness, genital and breast atrophy, a buffalo-type of obesity, moon facies, insulin-resistant diabetes, hypertension, mild hirsutism, purple abdominal striae, spinal osteoporosis, ruddy face, oily skin, and, often, an acneiform facial eruption. The urinary 17-ketosteroids are usually moderately increased but not necessarily so. The urinary 11-oxysteroids are often markedly elevated. By contrast with the adrenogenital syndrome, there is apparently an overproduction of the steroids concerned with gluconeogenesis rather than an overproduction of the androgenic or mas-

During the same year, Greenblatt[4] reported on a series of amenorrheic, hirsute women who responded to cortisone therapy. He postulated that the effect of the cortisone was not due merely to its depressant action on 17-ketosteroid excretion through its inhibition of adrenocorticotropic production, but to a balancing action of growth hormone and adrenal steroids, so as to permit a more orderly release of pituitary gonadotropins. In 1954, Van de Wiele and associates[13] studied a group of women with idiopathic hirsutism and also found that some of them showed increased dehydroisoandrosterone and 17-ketosteroid excretion levels, which dropped after cortisone administration. They postulated that the hirsutism of the group with elevated levels was probably due to adrenocortical hyperfunction, whereas the others with normal 17-ketosteroid values were possibly either constitutionally normal or their hirsutism was of ovarian origin. In 1956, Kappas and his associates[14] were among the first to show biochemically that idiopathic hirsutism was probably characterized by the *selective hypersecretion of an adrenal androgen*. They were able to control this hypersecretion by administration of cortisone and advanced the concept that these patients bore a "transitional" relationship to the adrenogenital syndrome. They stated that the elevated levels of this adrenal androgen were probably reversible, with treatment, to essentially normal urinary steroidal values.

Recently, a thorough study of 45 women with hirsutism was carried out by Perloff and his associates.[15] The study group was compared to a group of 16 normal women, with respect to various clinical and laboratory findings. Clinically, these 45 women were further subdivided: (1) those with hirsutism alone and normal menses—16; (2) those with hirsutism plus abnormal menstrual function—22; and (3) those with a surgically verified Stein-Leventhal syndrome—7. In addition to a comprehensive clinical and laboratory investigation of each patient, particular attention was paid to the levels of urinary ketosteroids. In many of these patients, results showed that the levels of the total neutral ketosteroids, as well as those of the strongly androgenic $C_{19}O_2$ fractions, correlated in some measure with the degree of hirsutism present. In addition, it seems that some women with idiopathic hirsutism have hair follicles which are more sensitive to serum androgen. In fact, hair growth of this type is often associated with increased pilosebaceous activity and acne vulgaris, so that either one or both dysfunctions appear first at puberty.

In Perloff's patients, the administration of prednisone in daily doses of 7.5 to 15 mg. reduced the total neutral 17-ketosteroid and the $C_{19}O_2$ fractions to normal or almost to normal levels.

> He reported that fair to good improvement in hirsutism was noted in all patients treated with prednisone, but different areas responded variously. Hair on the chin, thigh, and, occasionally, upper lip was most resistant, whereas that on the sides of the face disappeared most quickly and completely. Three to four weeks after initiation of therapy, wax depilation was performed, and this was repeated as frequently as required. After approximately six months, any coarse hair which remained, usually under the chin, was removed by electrolysis. The incidence of recurrence is not known; however, in three patients it commenced immediately after cessation of therapy, and prednisone was readministered.

It is of interest that prednisone, when administered in daily doses of 5 to 10 mg. to normal persons, produced typical hirsutism of Cushing's type or acne or both, according to Perloff. This did not occur in any patient who originally had elevated $C_{19}O_2$ levels.

As a result of their studies of idiopathic hirsutism, Perloff and his associates[16] postulated the following sequence of events as a theoretical causative mechanism.

> (1) increase in corticoid requirements, as at puberty; (2) relative insufficiency of hydrocortisone production owing to a deficiency of chemical precursors or adrenal enzymatic defects; (3) inadequate level of blood corticoids; (4) pituitary gland release with production of larger than normal amounts of adrenocorticotropic hormone (ACTH); (5) increased stimulation of adrenocortical function until hydrocortisone production becomes adequate, but, simultaneously; (6) excessive synthesis of androgen, resulting in the urinary hormonal pattern found in our patients, i. e., normal levels of corticoids and their derivatives, and elevated androgens and their metabolic end-products.

The conclusions from these studies strongly fortify the belief that hirsutism of this type is due to primary changes in the adrenals.

Other investigators have not had as good results in patients with ordinary or idiopathic hirsutism as did Perloff and his group. In fact, it would seem desirable to restrict steroid therapy to those patients with elevated 17-ketosteroid levels and to avoid the administration of these drugs (even in these "comparatively safe," low doses) to women whose only complaint is hirsutism. If the hirsutism is combined with other endocrine changes (both chemical and physical) plus elevated 17-ketosteroid levels, plus elevated $C_{19}O_2$ fractions, the possibilities of a therapeutic result are greater. It should be kept in mind that dramatic changes in hirsutism among these women do not usually occur. Unfortunately, once the pilary system has been activated, it is very difficult to modify it. From my observation, the growth of hair can be diminished so that, in women who require daily shaving, the interval may be lengthened and the number of times that shaving is required may be reduced to three times weekly. It is also advisable to employ concurrent electrolysis in order to remove the hair growth already present. If electrolysis has failed previously, it becomes a feasible process when combined with administration of steroids. In addition to steroid therapy, Greenblatt advises the administration of potassium chloride (300 to 600 mg. daily), small amounts of thyroid extract (30 to 60 mg. daily), and a high-protein, low-salt diet.

syndrome frequently overlaps the adrenogenital group. According to these authors,[5] the following signs and symptoms aid in the differentiation of "pure" Cushing's syndrome, "pure" adrenogenitalism, and the Stein-Leventhal syndrome: in the first, muscular weakness and pseudomasculinization; in the second, increased strength and true virilism; and in the third, hirsutism with marked femininity.

Acromegaly is due to hyperfunction of the eosinophilic cells of the anterior lobe of the pituitary gland. It is characterized by an enlargement of the peripheral parts of the body (hands, feet, nose, and jaw) caused by excessive secretion of growth hormone during adult life. Hirsutism occurs in many of these patients, although it is not a paramount feature. Surgical, medical, and radiation therapy may be of some value in these patients.

The combination of hirsutism and diabetes mellitus was called Achard-Thiers syndrome and was formerly considered a specific syndrome. The association is now classified as a not-uncommon, coincidental occurrence due to the frequency of both diseases.

Adiposogenital dystrophy, also known as Frohlich's syndrome, is a rare disease due to a functional disturbance of the pituitary-hypothalamic region and characterized by hypogonadism and obesity. Hypertrichosis may appear on the face and extremities. When this disease is caused by a tumor, the treatment is surgical. The other cases do not respond well to therapy.

Miscellaneous and Borderline Endocrine Types.—Hirsutism sometimes occurs in association with a number of uncommon and miscellaneous types of endocrinopathy. These include testicular tumors (especially interstitial-cell tumors and, occasionally, embryonal types), juvenile hypothyroidism, malignant thymomas (causing so-called Cushing's syndrome [?]), pancreatic carcinoma (causing so-called Cushing's syndrome [?]), metabolic craniopathies (pineal and hypothalamic tumors resulting in excessive secretion of pituitary gonadotropin [?]), polyostotic fibrous dysplasia (Albright's syndrome), the starvation state ("hibernation" syndrome), the Morgagni-Stewart-Morel syndrome [5] (headache, frontal bone hyperostosis, virilism, obesity, mental changes), and other uncommon entities.

Methods of Hair Removal and Cosmetic Management

The preceding discussion has presented a review of the causes of hirsutism as well as its medical and surgical management. The final portion of this report will concern itself with a brief review of systemically administered agents (other than hormones), which have a depilatory action, and a survey of the various methods available for the external removal of hair. These include (1) chemical agents (including drugs) administered internally and (2) external methods of hair removal or cosmetic management such as (*a*) tweezing, clipping, or shaving, (*b*) pumice, (*c*) waxes, (*d*) bleaches (for lightening color; no depilatory action), (*e*) depilatories (chemical), (*f*) electrolysis and electrocoagulation, and (*g*) ionizing radiations.

Chemical Agents (Including Drugs).—The ingestion of certain chemicals results in a specific depilatory action due to a direct toxic effect on the epithelium of the hair follicle.[3] Thallium acetate is used for the purpose of temporary epilation in patients with ringworm of the scalp in some countries other than the United States. Since this drug has severe toxic manifestations (primarily via the central nervous system), it is not considered safe, and it is definitely not advised for the cosmetic removal of excessive hair. Furthermore, recent studies with a new antifungal agent, griseofulvin, indicate that it will be the drug of choice in the treatment of tinea capitis (ringworm of the scalp). Formerly, thallium acetate was used in cream form as a depilatory; this usage is mentioned only to be condemned due to its potentially dangerous side-effects, which include cataract formation and various neurotoxic manifestations.

Tweezing, Clipping, or Shaving.—For the temporary removal of an occasional hair or hairs, either tweezing, clipping, or shaving is adequate. Proper hygienic measures should be used such as washing the area with an antiseptic soap before and after hair removal and the use of an astringent, antiseptic, wet dressing if a larger area is included. Tweezing hairs in the vicinity of the body orifices (e. g., the nose) should be performed with caution, if at all, and always with strict asepsis. For temporary hair removal in large areas such as the axillas and legs, electric razors as well as ordinary safety razors have become increasingly popular. Despite many popular notions to the contrary, cutting or shaving hair will not permanently stimulate hair growth. If it did, shaving the male scalp would have become a very popular custom.

Pumice.—Pumice, which is volcanic glass, is full of minute cavities and is very light in weight. Although primarily effective as a polishing agent, it can be used as a simple method for the removal of hair, merely by mechanical friction over the hairy site. Subsequent to its usage, a bland emollient should be gently massaged into the area to lessen the irritation of the skin produced by the pumice and friction.

Wax.—As a method of hair removal, wax has been used for many years. Prior to application, the skin is washed with soap and water and dried. The wax, which is usually a mixture of rosin and beeswax (sometimes modified with mineral oil or other waxes), is melted and applied, while still warm, to the hairy area. After the application, the wax culinizing hormones. Pure syndromes are not common due to admixtures of the adrenogenital component. The therapy is surgical if the diagnosis of a tumor of the adrenal cortex has been established. In patients with adrenal hyperplasia, the treatment of choice appears to be bilateral adrenalectomy followed by adequate postoperative management often similar to that of the patient with adrenal cortical hypofunction. This method appears to have advantages over previous measures used, such as roentgen irradiation of the anterior pituitary and the use of sex steroids.

Hirsutism of Ovarian Origin.—Major endocrine changes of ovarian origin result in the occurrence of one of two syndromes, with characteristic hirsutism. These may be identified on the basis of the presence or absence of virilization. The virilizing types are due to masculinizing ovarian tumors. The major members of this group are the arrhenoblastomas, adrenal rest tumors, and the hilar cell (Leydig cell) tumors. The major organic lesion of the ovaries responsible for hirsutism, virilism, and amenorrhea is an arrhenoblastoma.[5] Other less common types of masculinizing ovarian tumors include those due to theca-cell hyperplasia and diffuse, ovarian luteinization. The symptoms depend on the age of the patient and the activity of the tumor. In childhood, these tumors are clinically manifest by a precocious and masculinizing pseudopuberty or by so-called Cushing's syndrome. In the adult, the manifestations are those of the adrenogenital syndrome, so-called Cushing's syndrome, or mixtures of both. The overproduced hormones are essentially androgens, their metabolites, and possibly all adrenocortical hormones. De Alvarez and Heitman observe that the 17-ketosteroid urinary excretion is not strikingly elevated in patients with arrhenoblastomas.

The second group of hirsute patients with ovarian dysfunction presents an entity now classified as the Stein-Leventhal syndrome. This syndrome is characterized by amenorrhea, obesity, sterility, and symmetrically enlarged ovaries. About half of these patients have hirsutism, but virilism does not occur. Small breasts and uterine hypoplasia are common among patients with this disorder. The diagnosis is usually made on the basis of physical and pelvic findings and preferably confirmed by pneumoroentgenography or laparotomy. According to Stein, the urinary 17-ketosteroid excretion is normal (8 to 11 mg. in 24 hours), and he claims that this finding distinguishes this disorder from the adrenogenital syndrome (20 mg. or more in 24 hours). However, in the recent report by Perloff and associates,[15] seven patients with surgically proved Stein-Leventhal syndrome showed a mean urinary 17-ketosteroid excretion of more than 20 mg. in 24 hours. Furthermore, the urinary levels of the $C_{19}O_2$ fractions were elevated in every patient, whereas those of the $C_{19}O_3$ fractions were normal in four of the six subjects, suggesting that the latter measurement is less reliable in differentiating patients with hirsutism and Stein-Leventhal syndrome from normal patients. The $C_{19}O_2$ urinary excretion levels correlated even more closely with the degree of hirsutism than with the presence of a Stein-Leventhal syndrome. The treatment of this syndrome, according to Stein, is surgical. The recommended operation consists of a wedge resection of the enlarged ovaries, puncture of the cystic follicles from within the incision, and careful suture. Perloff and his group, as well as other investigators, advise a trial with prednisone for at least 6 to 12 months before surgery. If the menstrual status improves, therapy should be continued for longer periods, and the scheduling of ovarian wedge resection (if it is to be done at all) must depend on the judgment of the clinician. These investigators suggest that the dosage be regulated by the physician according to his clinical observation of the patient and by monthly evaluations of the patient's urinary 17-ketosteroid levels. The total neutral ketosteroid levels should be maintained between 6 and 10 mg. and the level of the $C_{19}O_2$ fraction should be suppressed below 5 mg. The prednisone therapy should be initiated with a dosage of 10 mg. per day and adjusted by increments of 2.5 mg. In their studies, hirsutism responded well to this treatment, and the menstrual abnormalities improved. Stein claims that prolonged endocrine therapy before surgery lessens the possibility of good operative results.

Perloff and his group state that there is a dramatic reduction of levels of total and fractional 17-ketosteroids after prednisone therapy but relatively small change in these levels incident to ovarian surgery. There is improvement in menstrual status but not in hirsutism after wedge resection of the ovaries, whereas treatment with prednisone produces beneficial effects on both hirsutism and menstrual function. These facts, together with the association of adrenocortical hyperfunction and Stein-Leventhal syndrome, seem to indicate that the adrenal disorder is primary and that ovarian changes either follow or develop concurrently.

Hirsutism of Pituitary Origin.—Major endocrine changes of pituitary origin which produce hirsutism do not result in virilization. Pituitary basophilism (Cushing's disease) is due to a basophilic adenoma of the anterior lobe of the pituitary gland. It is an uncommon disease, and its clinical manifestations are those due to hyperfunction of the adrenal cortex. De Alvarez and Heitman state that it is an expression of an excessive adrenocortical secretion of the 11, 17-oxygenated corticoids, hydrocortisone, and cortisone. The hirsutism is usually not associated with other virilizing changes, although the of certain skin disorders and for the production of temporary epilation in cases of ringworm of the scalp, it should never be employed for the purposes of cosmetic removal of excessive hair. It has been mentioned only to be condemned for this particular usage.

Summary

In so-called idiopathic hirsutism, the administration of small amounts of the steroid hormones (subsequent to thorough diagnostic and endocrinologic case study) is sometimes an effective remedial measure. Certain measures for the external control of hirsutism include depilatories, waxes, and bleaches, as well as physical techniques such as electrolysis.

2 E. 69th St.

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SCHIZOPHRENIA IN CITY NEIGHBORHOODS.—Faris and Dunham made a thorough study of the differences in the numbers of hospital admissions for specific illnesses, including schizophrenia, in different neighborhoods in Chicago. They also utilized earlier findings from other cities. Later studies which followed their lead have tended to confirm their findings. The fact has thus become established that there is a very marked difference in the frequency of hospital admissions for schizophrenia from different city neighborhoods. A consistent pattern has prevailed, at least in the United States in recent decades: Admission rates from socioeconomically low central districts are high; those from socioeconomically high suburban districts are low. The proportion of maximum to minimum rates may be as high as 10:1. . . . The *drift hypothesis* states that schizophrenics have a tendency to drift into the socioeconomically lower sections and that this explains why a relatively larger number of them are admitted from these sections. The *breeder hypothesis,* in contrast to the drift hypothesis, states that the character of the neighborhood is causally related to schizophrenia; i. e., that by living in those neighborhoods individuals are more apt to develop schizophrenia. . . . If we were in a better position to see the dynamics by which a type of neighborhood can foster the development of schizophrenia in individuals who live there, we would be able to derive the full benefit that ecology can furnish for understanding, and eventually for better control, of schizophrenia.—R. Plank, Ecology of Schizophrenia: Newer Research on the Drift Hypothesis, *American Journal of Orthopsychiatry,* 1959.

is permitted to cool and then is removed with a single fast movement. The depilated area is then cleansed again, and a bland, antiseptic lotion (or cream) is applied. The process is not unlike the application and removal of a strip of adhesive tape.

Bleaches.—Although bleaching agents do not remove hair, they do render it less conspicuous. Bleaching solutions are usually combinations of ammonia and peroxide. A typical formula contains 5% of a 30% solution of hydrogen peroxide and 4% of diluted ammonia solution, U. S. P., in water. Various mixtures in liquid, ointment, or oily vehicles are available. The bleach is applied to the hair site for a specified length of time, depending on factors such as the strength of the bleach and the sensitivity of the skin underlying the hairy area. After removal of the bleach, a bland lotion or cream is sometimes necessary. The combined use of ammonia and hydrogen peroxide often makes the hair brittle; it thins and breaks—a beneficial effect in hirsutism. Also, various hair dyes may be used for the purpose of modifying the color of hair appearing elsewhere than on the scalp proper. Their use for this purpose is generally not advisable because of the possibility of irritation or sensitization of the underlying skin.

Depilatories (Chemical).—The term "depilatory" is applied to preparations designed for the temporary removal of unwanted hair, especially of the axillas and the legs. Such preparations should have a minimal incidence of skin sensitization or irritation despite constant and regular usage. The advantage of such preparations over shaving is that, instead of merely cutting the hairs at the skin surface, it removes them at or below the mouth of the hair follicle. As a result, the next application is unnecessary for several weeks, whereas with simple shaving, a dark growth is evident within a few days.

The depilatories in popular usage are of two main types. Those containing barium or stronium sulfide, or a derivative, are very effective and work in a few minutes after application. Occasional instances of sensitization or irritation from these preparations do occur, and they give forth an odor of hydrogen sulfide, but otherwise they are quite acceptable. Other types are based on the use of substituted mercaptans in the presence of alkaline-reacting materials (for example, calcium thioglycollate). These preparations have the advantage of possessing a less offensive odor than the sulfide type; however, they have the disadvantage of taking more than twice as long to depilate the hair. So far as skin irritation or toxicity is concerned, there is little difference between them.

Electrolysis and Electrocoagulation.—Up to the present time, the only successful and permanent method of external hair removal is the destruction of the papilla by electrical methods. When properly performed, this technique results in the permanent removal of hair from large areas of the body surface. It must be performed under proper conditions of asepsis in order to prevent infection and scarring. One method consists of cleansing the skin with a bactericidal soap, followed by the application of 70% alcohol both before and after the procedure. Of primary importance is the requisite for a skilled and well-trained operator, also to prevent infection and scarring. Unfortunately, the laxity of the laws in many states results in just the reverse. For this reason, it is generally considered advisable to restrict this technique to competent, medical personnel, with adequate training in both the hygienic and technical aspects of the procedure. It is not the purpose of this report to dwell on the minutiae of the technical procedure itself, inasmuch as these may be found in certain specialized dermatological texts and articles. However, in brief, there are two types of electric methods in use at the present time. The first employs a galvanic current usually generated from a small battery unit. The intensity of the current, the time of contact, the depth of insertion, and many other factors of technical significance are matters of experience and skill.

The second method, which is actually not the same as electrolysis, employs a diathermy current (high frequency, electrocoagulation) and is more popular at the present time because it is a faster technique (about 500 hairs can be removed in one hour). Both methods are capable of producing infection and scarring. It is emphasized that training, skill, and scrupulous attention to local hygiene are fundamental. Even with the best technique, a recurrence of approximately 15 to 25% of the epilated hairs is to be expected, but, with continued diligence, these can eventually be removed. Electrolysis and electrocoagulation are very useful modalities, and the cosmetic and psychological results of their employment are extremely satisfactory in most cases.

Radiation.—X-ray probably affects hair growth by interfering with mitosis. Although ionizing radiations can be administered to the skin, with resultant permanent destruction of the hair follicle and loss of hair, this treatment is not safe for cosmetic usage. The reason for this is that the amount of radiation required to destroy the hair follicle permanently will also produce certain permanent and irreversible changes in the skin itself. In the past and during the present medical era, an occasional article has appeared claiming satisfactory results in the treatment of hypertrichosis by means of x-ray therapy or some related form of ionizing radiation. These reports have never been confirmed by qualified observers and, in fact, late sequelae of such treatment are still being observed. These sequelae range from chronic radiodermatitis of the skin to epitheliomatous change, and even death. Therefore, whereas x-ray therapy is a useful modality in the treatment problems of mobilizing the economic resources needed to bring rehabilitation services to those who need them.

Characteristics of Rehabilitation Centers

The relationship of medicine to the problem of paying for the services of rehabilitation centers can be intelligently viewed only in the perspective of the interactions between the practice of medicine and the operation of centers as a whole. It might be well, therefore, briefly to identify the basic characteristics of rehabilitation centers.

Rehabilitation centers generally fall into several groups: (1) privately operated community centers (established and directed by boards of prominent community leaders from various walks of life) which constitute the bulk of the centers in the United States, (2) centers operated as part of hospitals, including those connected with teaching hospitals of medical schools, and (3) state-operated centers, which are primarily vocational in purpose. Almost all of the facilities provide services on an outpatient basis; a minority of these institutions offer services on an inpatient and ambulatory basis. Among centers, there is also considerable range in program emphasis. The majority of facilities concentrate on problems of physical restoration, whereas others specialize in the vocational problems of rehabilitation. Centers also differ in the degree to which they are equipped to deal with the emotional and social factors influencing the lives of handicapped persons. Yet, all centers and facilities have in common the purpose of bringing together various professional skills, supportive personnel, needed equipment, and the proper space to accomplish rehabilitation.

Medicine's Role in Development and Finance

What is medicine's part in the healthful development and sound financing of rehabilitation centers and facilities? The growth of rehabilitation centers presents medicine with opportunities that are broadening its effectiveness and influence and, also, presents the physician with a number of new relationships and responsibilities. Bringing the benefits of rehabilitation to his patients and the successful financing of the services needed by his patients depend on how the practicing physician accepts the challenge of rehabilitation and, therein, fulfills the new roles and responsibilities. Representatives of the medical profession play three influential roles vitally affecting the functioning of rehabilitation centers and facilities.

Role of Physician.—The practicing physician has the key role of referring all or nearly all of the patients to our nation's rehabilitation centers. Almost all rehabilitation centers, as a matter of policy, require a written referral from a physician before they will accept a patient. The services of most centers, with few exceptions, are offered to private physicians and their patients. The physician, therefore, is the person the centers rely on to recognize the patient's need for rehabilitation services and to bring the patient and these services together. The physician also plays an indispensable role in the success of the rehabilitation programs of his patients, for he is responsible for supervision of the medical phases of his patients' rehabilitation. He may also play an important part as personal counselor in the interpretation of the other phases of rehabilitation to his patients, and he is expected to provide follow-up of the cases after his patients are discharged from the center.

Role of Medical Director and Advisory Committee.—Formulation and supervision of the medical policies and direction of the medical services of rehabilitation centers are medical responsibilities. Most rehabilitation facilities, in cooperation with their county medical society, have established a medical advisory committee to guide them in matters of medical standards and policies. In many centers, the position of medical director has also been established to provide day-to-day supervision of medically related services and to assist in the development of the rehabilitation services needed by the community.

Role of Board of Directors.—Physicians also serve as members of the boards of directors of centers in their capacity as prominent citizens and leading professional men in their communities. In this role, physicians are responsible for the planning and direction of the steps requisite to establishing and operating the services essential to meet the needs of handicapped citizens. Representatives of the medical profession are, therefore, deeply involved in the sound development of rehabilitation center services. In each of their roles, they play a vital part in mustering the economic strength that is so essential to sound growth of medical and other rehabilitative services.

Available Community Resources

How can the private physician help his patient (especially the patient with limited means) obtain the costly services of a rehabilitation center? The answer to this question varies somewhat from community to community, but, in general, many of the same financial resources are available to patients in different communities. A physician's knowledge of these resources may spell the difference between obtaining the needed services for his patient or not.

Third-Party Agencies.—The local affiliates of voluntary health agencies, state vocational rehabilitation agencies, and insurance companies carrying workmen's compensation and health and accident insurance have programs to buy rehabilitation services for patients. Some of these agencies make referrals directly to centers, but most of them also of the meager information available, does not appear to differ significantly from the latter or from other barbiturates with a similar duration of action. According to older studies in which white rats and rabbits were used, its efficacy and toxicity are in the upper range of the group. (See the section on barbituric acid derivatives in New and Nonofficial Drugs.) The metabolic fate and routes of excretion of talbutal are unknown. Although the drug has had only minimal experimental study with respect to potential toxicity, no serious adverse effects have accompanied its clinical usage over a period of several years. The same precautions applicable to the use of other barbiturates should be observed with talbutal.

Dosage.—Talbutal is administered orally. For sedative effects, 30 to 50 mg. is given two or three times a day. The hypnotic dose is 120 mg., given 15 to 30 minutes before the onset of sleep is desired.

Preparations.—tablets 30, 50, and 120 mg.

Year of introduction: 1955.

Winthrop Laboratories, Division of Sterling Drug Inc., cooperated by furnishing scientific data to aid in the evaluation of talbutal.

COMMITTEE ON REHABILITATION

The following report is the sixth in a series of articles which have been authorized for publication by the Committee. The first five appeared in The Journal *on Oct. 24, Nov. 7, Nov. 21, Dec. 12, 1959, and Jan. 9, 1960, pages 1107, 1359, 1694, 2098, and 163. This series deals with various aspects of rehabilitation which are of interest to physicians.*

Ralph E. De Forest, M.D., *Secretary.*

PAYING FOR REHABILITATION

Dean W. Roberts, M.D.

and

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One of the most important manifestations of the growth of the rehabilitation program has been the development of rehabilitation centers and facilities offering a wide range of professional services to meet the needs of handicapped persons. The rapid emergence of these facilities in hundreds of American communities since the end of World War II is of vital interest to the medical profession and, in particular, to the practicing physician. The services furnished by these centers have expanded substantially the resources available to the profession for dealing with the problems of disability. These centers have enlarged the aggregate of trained personnel, new techniques, and facilities which the physician can muster to serve his patients. The development of rehabilitation centers has also had the far-reaching effect of expanding both the influence and responsibilities of the medical profession; physicians are working with the many professional and community groups which are playing such an important role in the development of rehabilitation resources.

The medical profession has performed an important part in the development of rehabilitation centers and facilities; it is now being called on to play an increasingly larger role in the use and guidance of these institutions.

Recommendations of Committee on Rehabilitation

In December, 1958, the House of Delegates of the American Medical Association endorsed a recommendation of the A. M. A. Committee on Rehabilitation, encouraging state and county medical societies to assume greater leadership to meet the problems of the disabled and handicapped. The Committee recommended that "the medical profession take a direct interest in local rehabilitation programs, since it is the individual physician's responsibility to see that his patients receive the rehabilitation service they need and to direct them to local available facilities."[1] Furthermore, it stated, "the medical profession should initiate the leadership necessary to see that adequate rehabilitation facilities and services are available locally."[1]

The private physician and the medical profession as a whole have a responsibility to use rehabilitation services and to provide the leadership needed to gather the resources available for rehabilitation of those in need of such services; in addition, as physicians and community leaders, they have a further responsibility to help solve some of the difficult

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Strengthening the financial position of rehabilitation centers and, thus, ensuring the growth of the rehabilitation services to meet the needs of the handicapped and chronically ill depends on developing sufficient third-party sponsorship of patients to recover an increasingly larger share of the costs of rehabilitation services. The only practical way in which centers can reduce their dependence on gifts and grants and other forms of subsidy is through an increase in the payments for services made by third parties. Prepayment has made it possible to increase payments to nonprofit general hospitals for patient service to almost 90% of all operating income—from 71% in 1935 to 89% in 1952.[3] Today, this figure is undoubtedly higher. The bulk of this income comes from third-party payments.

The cost of rehabilitation, like the cost of hospital care, is higher than the average family can afford. Moreover, persons requiring rehabilitation services usually are less able to pay for such services than persons needing hospital care, for the long-term nature and severe impact of disability exhausts the economic resources of most families. What financial resources they might have usually are spent during the acute stage of disability. Rehabilitation centers and facilities are, therefore, no more able to derive a major portion of their charges directly from patients and their families than are hospitals.

In reporting to the nation in 1954, the Commission on Financing Hospital Care observed, "the financial stability of the voluntary hospital system is becoming increasingly dependent upon the degree to which voluntary prepayment enables both the general public and hospitals to meet their common problem of financing hospital care."[4] It has been said that the hospital administrators of 1975 will take it as much for granted that 90% of their income will come from well people as the administrators of 1925 took for granted that 90% of their income came from sick people.

These findings graphically point up the need to develop far greater prepaid insurance and other means to make the services of rehabilitation centers available to patients who need them. The financial problems retarding the development of rehabilitation services cannot be adequately solved until rehabilitation is brought into the mainstream of voluntary prepayment of medical and health services. Today, the financing of rehabilitation services stands almost wholly outside voluntary mechanisms of prepayment. By contrast, over 120 million persons in 1957 (more than 70% of the total population of the United States) were protected against hospital expenses by some form of voluntary prepayment.[5]

Outpatient rehabilitation services are excluded from prepayment coverage partly because voluntary prepayment plans have not met the problem of financing medical and health services provided outside the hospital. However, application of the insurance principle to the inpatient phases of rehabilitation also is in its infancy. The encouraging efforts being made by Blue Cross plans and insurance carriers to develop rehabilitation coverage for their members are only a bare beginning.

Summary

Physicians, in their roles as referring doctors, medical directors, members of medical advisory committees, and as members of boards of directors of rehabilitation centers and facilities, can do much to assist in developing sound financial support of the centers and facilities that they use and guide. Full realization of the potential benefits of rehabilitation depends, in large measure, on the leadership which organized medicine and individual physicians give to the organization and financing of rehabilitation services. Doctor Henry Kessler has said, "The physically handicapped are extraordinary in that they seek but an ordinary destiny."[6] Medicine owes the disabled patient nothing less than full mobilization of its professional resources and influence to help him realize this humble destiny.

TABLE 2.—*Per Cent of Total Operating Income from Subsidy and from Charges in Ten Rehabilitation Centers, 1958-1959**

	Income, Av. %	
	Subsidy	Charges
All Centers	41	59
Inpatient Centers	18	82
No. 1	18	82
No. 2	18	82
No. 3	26	74
No. 4	26	74
No. 5	4	96
Outpatient Centers	63	37
No. 1	73	27
No. 2	59	41
No. 3	56	44
No. 4	56	44
No. 5	73	27

* Data are based on 12-month period during 1958-1959.

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support cases brought to their attention by private physicians. Referring physicians also should consult admitting officials of rehabilitation centers and facilities, as such officials are familiar with the resources that are available in their community to sponsor patients who are in need of rehabilitation services.

Donations from Individuals or Organizations.—The limitations in funds available to purchase services for patients who do not have adequate financial resources should not deter a physician from referring his patients to a rehabilitation center when its services are needed. Most rehabilitation centers provide some services to patients at reduced rates or at no cost, if necessary. Because the sources of third-party support (together with private fees) have not been adequate, public-spirited citizens and organizations make substantial gifts, donations, and grants to centers to pay for services for the disabled. Increased use of the rehabilitation facility in the community, although it may tax existing funds for rehabilitation, certainly will strengthen the efforts and possibilities of developing more adequate financial support for rehabilitation center services. Failure to use existing resources may have the opposite effect.

TABLE 1.—*Average Cost Per Daily Outpatient Visit in Ten Rehabilitation Centers**

	Cost
All Centers	$ 7.28
Inpatient Centers	
No. 1	6.90
No. 2	9.85
No. 3	7.90
No. 4	10.15
No. 5	3.45
Outpatient Centers	
No. 1	8.55
No. 2	7.71
No. 3	5.99
No. 4	7.14
No. 5	10.31

* Based on two-week or four-week study period, 1958 or 1959.

Study Findings

Who pays for rehabilitation? Rehabilitation is expensive, and, like hospital care, it is increasing in cost. Charges for inpatient care in many centers average about $30 a day, and charges above $30 a day are not unusual. The findings of a study being conducted by the National Society for Crippled Children and Adults show that the average cost of a daily outpatient visit in 10 nationally prominent rehabilitation centers was about $7 per visit, excluding the cost of a physician's services (table 1).[2] Services on an outpatient or ambulatory basis vary in cost, depending on the type of service rendered, but charges from $5 to $10 a visit are common. In many cases, these charges do not reflect the full cost of the service. Whereas there are a few rehabilitation centers which, as a matter of philosophy, do not charge for their services or charge well below cost, the great majority of centers, however, strive to recover, through charges, as much of the cost of service as they can.

The problem of paying for the services of rehabilitation centers and facilities is one of the most difficult issues facing the growth of rehabilitation services. Most rehabilitation centers and facilities have a constant struggle to raise sufficient funds to meet their regular operating expenses. The process of obtaining funds to pay these expenses usually requires much effort and often is a source of considerable strain on boards and officials of the centers. Whereas hundreds of centers meet their annual financial obligations and continue to grow, it is clear that the difficulties involved in obtaining adequate funds are retarding the healthy development of rehabilitation services.

Rehabilitation centers and facilities obtain the money it takes to pay for their services in two ways: (1) through charges for the services they perform and (2) through subsidy mainly in the form of contributions and grants. The difficulty rehabilitation centers face in obtaining sufficient income to recover the costs of operations arises from the fact that they do not obtain enough income from charges for their services. Therefore, they must annually seek contributions and grants to make up the difference. Few rehabilitation centers are close to being self-supporting through charges for their services. The centers serving inpatients have a less serious problem in this respect than those which only provide services to persons on an ambulatory basis. The difference, however, is one of degree. The findings of the National Society study show that, of the 10 centers participating in the project, those offering services to inpatients annually obtain one-fifth of their income from such sources as donations and grants, whereas the outpatient centers raise about three-fifths of their operating income in the form of subsidies (table 2).[2] Considerable variation was also found among individual centers in the extent of their dependence on gifts and other types of subsidy.

The proportion of income which rehabilitation centers are able to raise through charges for their services is governed largely by the adequacy of funds which they receive from such sources as insurance companies, prepaid plans, and agencies that have programs sponsoring rehabilitation services for the disabled. A striking fact is revealed by the National Society study; third parties (not patients or their families) pay the overwhelming share of the fees collected for rehabilitation services. Moreover, the significantly higher degree of self-support achieved by centers offering inpatient services is accounted for by the fact that these centers derive the overwhelming share of their operating income from fees paid by third parties.

in a patient with acute appendicitis and a description of the postmortem examination preceded the modern description by Reginald Fitz by more than three hundred years. As a clinician, Fernel used the term *lues venerea* for the first time to describe clinical syphilis. A very readable biography of Fernel was written by Guillaume Plancey, for 10 years his associate, who lived in his home and thereby experienced an unusual opportunity to write of his master from intimate contact. The biography by Plancey and other Ferneliana was compiled by Sir Charles S. Sherrington [1] of Cambridge and published in 1946. Critical review of this small volume has been a rewarding experience.

Fernel developed a passion for the humanities early in life and begged his father for permission to study rhetoric and philosophy in Paris. His father realized that "Just as the careful, good and productive soil promises a fine crop, so likewise with man and learning, passion for study and the budding of innate inclinations from youth up presage a maturity rich in bright accomplishment." After his receipt of a Master's degree, his brilliance was widely recognized by the faculty and he was urged to accept a position and to teach dialectic. He declined because he wished to be free to concentrate on the writings of Cicero, Aristotle, and Plato. "He resolved to forgo entertainment, convivialities, feasts and drinking bouts, and even talks with fellow students and acquaintances. He took account neither of food nor sleep nor exercise, of ailments and affairs; he put up with everything in order to attain knowledge of the liberal arts—he had no other delight than learning. He thought every hour lost which was not spent in reading and studying with good authors. Desire for learning filled his mind; he was in love with scholarship and knowledge."

In the cultivation of his mind, Fernel spent the morning in mathematics; the afternoons were devoted to philosophy, and after the evening meal, attention was given to the Latin classics. Thus his training was at least the equivalent of a doctorate in philosophy before he turned to medicine as a career—but not completely so. Even between his hours given to the study of medicine he found time to teach mathematics. He had passed his 50th birthday before he devoted himself exclusively to the teaching and practice of medicine. When he finally established himself in medical practice, he attained renown in a few short years as the foremost physician in France, probably in Central Europe. Catherine de Médicis employed his services to cure her of sterility, and with this accomplishment he became her physician and delivered her 10 children, reportedly at a fee of 10,000 ecus each. His appointment as physician to his king, Henry II, he accepted with considerable reluctance because he feared that it would usurp precious time from his scholarly and professional opportunities.

His precepts of practice are worthy of emulation. Arising before daylight, he pored over his books until he breakfasted. Through the day he visited his patients, gave public lectures, and examined samples of urine that were brought to his office. After the evening meal he retired again to his study but did not sleep before midnight. Always an optimist in prognosis, he held out hope of recovery, in spite of overwhelming odds. In substance, he was a most successful physician and widely recognized as a skillful practitioner.

So much for his practice. He is equally famous through the centuries, however, for his contributions to physiology and pathology. There are chapters devoted to each of these subjects in his uncompleted monumental system of medicine. *De naturali parte medicinae,* published when he was 68 years of age, only four years before his death. There are no divisions in his physiology as we appreciate them today. The volume was prepared 80 years before Harvey's discovery of the circulation of blood. Neither chemistry nor the microscope were tools of his trade at that time. The four humors of Hippocrates were accepted. His conclusions on the digestive tract led Sherrington to suggest that some of the observations must have been performed on a patient whose esophagus or stomach had been injured accidentally and permitted direct inspection. His concept of circulation was pre-Harveyan. An original observation was a decrease in the size of the ventricles in systole, with a concomitant increase in the size of the great vessels. His "Physiology" went through 31 posthumous revisions in the next century.

His "Pathology" was his best-known achievement in medical writing. It was a systematic essay on morbidity, organ by organ throughout the body. The classification of disease was based on the premise that each disorder was specialized and confined to a localized site in an organ. Postmortem examinations were routine and at his death his body was prosected. A localized disease was a *simple* one when confined to a portion of one organ. The disease was *compound* when it affected an entire organ and *complex* when it affected two or more organs. The "Physiology" and "Pathology" of Fernel were in each respective subject the earliest systematic treatises. Each established its respective subject under this name. Each was the product of the same mind and hand. They were the companions as well as the building stones of a most successful practice of medicine by one of the great minds of France in the 16th century.

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1. Sherrington, C. S.: Endeavour of Jean Fernel, Cambridge University Press, 1946.

THE JOURNAL
OF THE AMERICAN MEDICAL ASSOCIATION

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THE FUNCTION OF VITAMIN B_{12} IN METABOLISM

THE structures of vitamin B_{12} and many related analogs are now known, yet the metabolic pathways requiring the vitamin have still to be characterized. Deficiency of the vitamin expresses itself with eloquence in man, producing a megaloblastic anemia and related blood changes, neurological lesions, and evidence of depressed nuclear maturation in the cells of the upper gastrointestinal tract and possibly in the liver. In lower mammals and in fowls, decreased rate of growth is the only constant expression of deficiency, and no changes in the blood or nervous systems are evident. This species difference is unexplained. In certain micro-organisms vitamin B_{12} requirements have been extensively studied, both in culture and in cell-free systems.

Many functions have been ascribed to the vitamin, but which are direct and fundamental and which are secondary is not at present clear. Attempts to relate structure to function have been generally unconvincing. It is not even known in what state vitamin B_{12} exists either in animal tissue or in bacteria. In organs and tissues it is widely distributed, emphasizing the possibility that it has a widespread role. The most attractive speculation is that it is bound to proteins and serves as a co-enzyme. Weissbach and others[1] have described a vitamin B_{12} co-enzyme obtained from rabbit liver and Propionobacteria, which they claim has high anti-pernicious anemia activity, but this finding is not yet firmly established. The same complex has been shown to be active in the conversion of propionate to succinate in cell-free extracts of Propionobacteria, a reaction requiring biotin and acetyl co-enzyme A.[2]

In animals and in those micro-organisms with the most stringent growth requirements, such as Ochromonas, the dibenziminazole group is essential for biological activity; replacement of it with a purine, as in pseudovitamin B_{12}, results in biologically inactive or almost inactive substances. These analogs, also, do not compete with vitamin B_{12} in intestinal absorption mediated by intrinsic factor. The low biological activity of these purine analoges may be due to their inability to link effectively with specific proteins in cellular systems.

There is good evidence that vitamin B_{12} is involved in transmethylation reactions in lower organisms, but in mammalian tissues there is no firm evidence of involvement in any particular metabolic pathways. Johnson and his colleagues[3] obtained some indication in vitamin B_{12}-deficient piglets that transmethylation from methionine was not impaired, whereas methyl transfer from glycine was.

Hematological remissions in pernicious anemia induced with folic acid (although neurological lesions were aggravated or precipitated) and in megaloblastic anemia of infancy with ascorbic acid suggested a relationship between vitamin B_{12} and these other vitamins. At one time it was thought that the interrelationship occurred in pathways of nucleic acid synthesis; folic acid being converted to folinic acid which influenced purine and pyrimidine synthesis, while vitamin B_{12} operated in the interconversion to nucleosides. Thus, thymidine and other desoxyribosides can replace vitamin B_{12} in cultures of Lactobacilli; however, thymidine is now known not to produce remissions in pernicious anemia, contrary to earlier reports.

More recently, Smith[4] has advanced the attractive hypothesis that vitamin B_{12} is intimately related to all protein synthesis and that the diversity of expression is due to induced failure of synthesis of many enzymes. No better evidence is at present forthcoming. It is to be hoped that further study of recently obtained anti-vitamin B_{12} analogs will throw more light on the action of this intriguing substance.

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[1] Weissbach, H.; Toohey, J.; and Barker, H. A.: Isolation and Properties of B_{12} Coenzymes Containing Benzimidazole or Dimethybenzimidazole, Proc. Nat. Acad. Sc. 45:521-525 (April) 1959.

[2] Stadtman, E. R.; Overath, P.; Eggerer, H.; and Lynen, F.: Role of Biotin and Vitamin B_{12} Coenzyme in Propionate Metabolism, Biochem. and Biophys. Res. Communications, Vol. 2, New York, Academic Press, 1960, pp. 1-7.

[3] Johnson, B. C.: Absorption and Utilization of Vitamin B_{12}, Symposium on Nutritional Aspects of Blood Formation, Am. J. Clin. Nutrition, 3:50-51 (Jan.-Feb.) 1955.

[4] Smith, E. L.: Biochemical Functioning of Vitamin B_{12}, Nature **181**:305-306 (Feb.) 1958.

PHYSIOLOGIST, PATHOLOGIST, PHYSICIAN

Jean Francois Fernel (L., Ioannis Fernelii), born in the purlieus of Paris in 1485 A. D., was one of the remarkable scientists of the 16th century. If Galen is credited with the earliest treatise on human physiology, Fernel rediscovered this discipline 13 centuries later. Fernel also prepared a treatise on pathology. A presentation of the clinical findings

ORGANIZATION SECTION

PROPOSED INTERNAL REVENUE REGULATIONS CONCERNING PHYSICIANS IN GROUP PRACTICE

January 21, 1960

Honorable Dana Latham
Commissioner of Internal Revenue
Internal Revenue Service
Washington 25, D. C.

Dear Sir:

In connection with proposed Regulations, Sections 301.7701–1, 2, and 3, the American Medical Association desires the opportunity to have its representatives testify orally at the public hearing and submits herewith, in addition, certain comments and suggestions.

We are concerned that the regulations in the form in which they were published in the Federal Register on December 23, 1959, are not likely to attain the desired objective of clarifying, for tax purposes, the distinctions between associations and partnerships.

Section 301.7701–1 (c) states that local law shall govern "in determining whether the legal relationships which have been established in the formation of an organization are such that the standards are met." State laws pertaining to associations and partnerships not only differ greatly, but in many states there are neither statutes nor adequate judicial precedents dealing with associations. The introduction of local law as a factor in determining the tax classification of organizations would only serve to create uncertainty and confusion.

The Internal Revenue Service and the United States Supreme Court have repeatedly recognized the intent of Congress to establish, in the Internal Revenue Code, a system of taxation having uniform application irrespective of state laws. The application of the regulations under the 1939 Code, dealing with associations, did not depend upon local law and there is no apparent or valid basis for injecting this factor into the present regulations, particularly in view of the above mentioned ambiguities and uncertainties which now exist in the law of associations among the various states. It would be unconscionable to subject identical or substantially identical organizations to different tax classification because of their geographical location. If the proposed regulations are adopted, this situation would exist with reference to medical groups which now regard themselves as partnerships and not associations, and vice versa.

In neither the *Kintner* nor the *Galt* cases did the courts rely upon the laws of Montana or Texas, respectively, in arriving at the conclusion that for Federal tax purposes these organizations should be considered as associations.

Section 301.7701–2 (a) (2) states that the determination as to whether an organization is to be treated for tax purposes as a partnership or as an association depends on whether there exists: (1) continuity of life, (2) centralization of management, (3) limited liability, and (4) free transferability of interests. Our comments and suggestions with respect to each of these standards are as follows.

Continuity of Life

Section 301.7701–2 (b) (2) provides in part:

> An agreement by which an organization is established may provide that the business will be continued by the remaining members, if one member withdraws, but such agreement does not establish continuity of life if under local law the withdrawal of a member causes a dissolution of the organization. Thus, there may be a dissolution of the organization and no continuity of life although the business is continued by the remaining members.

In *most* of the states there are no statutory provisions regarding associations and, thus, existing partnership laws would probably be applied. Section 31 of the Uniform Partnership Act provides that the death of a partner dissolves the partnership even though the partnership agreement provides for continuation of the business. Technically, where the business is continued after the death of a partner, a new partnership under state law is created.

One of the most confusing partnership questions which existed prior to the 1954 Code was whether a partnership could continue its existence after the death or retirement of a partner, or the taking in of a new partner. Section 708 clearly establishes that none of these events terminate a partnership *for income tax purposes*, unless it ceases to operate, or unless there is a change of 50% or more in partnership capital *and* profits within a 12 month period.

The proposed regulations include, as a test of continuity of life, the requirement that a determination be made under local law even though Congress in its wisdom saw fit to enact Section 708 to cure the confusion previously caused by a similar requirement.

Whether an organization meets the test of continuity of life to qualify as an association should be determined under the agreement by which it is established and operated without reference to local law.

GO WEST BUT NOT TOO FAR WEST

A survey of the constituents of treated water supplies in relation to the mortality from cardiovascular disease has revealed noteworthy findings. The study was prompted by the knowledge that the age-adjusted death rate from all causes varied considerably from state to state. Arteriosclerotic heart disease, including coronary disease, accounts for 43% of all cardiovascular deaths and about 50% of cardiovascular deaths in men in this country. A natural male death rate of 250.8 per 100,000 was exceeded in all New England states except Maine, all Middle Atlantic states, and selected areas elsewhere. The extreme values were 336.1 in New York state and 148.2 in New Mexico. According to Sauer and Enterline,[1] these data cannot be explained on the basis of quality of physicians or accuracy of death certificates. Also it would appear that racial background, local dietary habits, sources of food, and environmental stresses or strain do not vary enough to account for the differences. These interesting facts have been overlooked by the Jack Spratt School of the Theory of Atherosclerosis, which holds that hard fats make hard arteries and that men (and women) of this lipid-loving nation are eating themselves into early coronary graves.

With this basic information recently available, Schroeder, long interested in hypertension and cardiovascular disease, utilized the most modern statistical methods, including the electronic computer, to weigh hardness of water with mortality rate. The findings are published in this issue of THE JOURNAL. The age-adjusted average death rates from all causes, and especially coronary heart disease, state by state, provided basic data. Evaluation of 20 constituents of finished water and age-adjusted death rates for coronary disease in each of 163 large metropolitan areas in the United States, which vary from a low of 299.0 to a high of 826.8 per 100,000, in Caucasoid men aged 45 to 64 years, was the corollary phase of the statistical investigation.

Death rates from noncardiovascular causes were found to be distributed equally between hard and soft water areas without correlation. It appeared that cardiovascular death rates, on the other hand, might be influenced by hardness of potable water, while death rates from all other causes probably were not so influenced. Analyses of death rates from arteriosclerotic heart disease, including coronary disease, showed skewness and a correlation with hardness of water at significant levels. Statistical study of a number of constituents that make treated water hard revealed that magnesium, bircarbonate, calcium, sulfate, total solids, specific conductance, and pH were highly significantly correlated with these death rates. No significant distributions were found for a number of other factors. Pollution of our water by detergents, industrial wastes, sewage, and all the effluvia of modern life does not contribute to its hardness.

If a highly significant negative correlation between hardness of water and mortality from coronary heart disease is valid, where does one seek the Fountain of Youth? Ponce de Leon believed that he had discovered it in Florida. This state is in the upper third of the favored category of hardness. South Dakota, Nebraska, and New Mexico lead the list. Indiana is next, although geographically she seems out of place. Arizona, Iowa, Utah, Kansas, Wyoming, and North Dakota follow in this order. Will the spa return as a health resort? Will the Great Salt Lake be as popular as the Ganges? If hard water makes soft arteries, will it be the fad to consume water charged with calcium and magnesium? If we wish to be spared coronary heart disease it may be desirable for the center of the population of this country to move west at a faster pace. Go west, young man, but not too far west.

DROPSY

Dropsy is the malfunction of the digestive power in the liver and is called hydropsy from hydro which is water and pisis which is disease, whence hydropisis, as it were a watery disease. According to the opinion of the ancients its forms are three: ascites, hyposarca and tympanites. But treat none of these with the knife except the one which is called ascites, in order to draw off the water which is between the peritoneum and the intestine.

Therefore, when you wish to use the knife in the treatment of this type, do it in this fashion: press down at first on the belly with your hand so that all water descends to the pubic region. Then consider very carefully whether the generation of the water occurred from a part of the intestines or from the disease of the liver or the spleen.

After having made the perforation, introduce a brazen or silver tube so that the water may be evacuated by itself. Take care not to let it drain for any length of time, since perhaps by reason of the release of the animal spirit the patient may die, or he may suffer fainting and approach death. But drain it according to the amount of the patient's strength, and then withdraw the tube and stop up the hole. But on the next day drain it once again by the use of the tube if the strength of the patient will permit it; and you should continue to do thus until only a little remains.—The Surgery of Theodoric, vol. 2, books 3 and 4, translated by E. Campbell, M.D., and J. Colton, M.A., New York, Appleton-Century-Crofts, Inc., 1960, pp. 94-95.

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[1] Sauer, H. E., and Enterline, P. E.: Are Geographical Variations in Cardiovascular Death Rates Real? J. Chron. Dis. **10**:513 (Dec.) 1959.

"corporation" for tax purposes. The Court did not imply that associations which were unable to attain freedom from personal liability for their members should be considered partnerships for tax purposes.

The proposed regulations have introduced a novel concept by stating that "an organization has the corporate characteristic of limited liability if there is no member who is personally liable for the debts of or the claims against the organization" and then going on to say that for this purpose "personal liability does not exist when the only members who are personally liable for the debts of the organization have no substantial assets which could be reached by a creditor of the organization."

Apparently, an Internal Revenue agent in applying this as a test to determine whether a medical clinic is a partnership or an association would require a statement of assets from each of the associates. What standard the agent would apply in determining whether a member has "substantial" assets is not indicated.

The proposed regulations recognize that limited liability is not a valid standard for the purpose of determining whether a trust is a "corporation" for tax purposes. However, they apparently overlooked the fact that since an association does not have the attribute of limiting liability, and it is specifically included in the Code as being within the term "corporation," limited liability is not a valid test.

Transferability of Interests

Section 301.7701–2 (e) provides a standard which is unreasonable and one which would require greater freedom for the transfer of a member's interest in an association than is frequently found in corporations.

Except for publicly held corporations, the transferability of shares in corporations is frequently subject to special restrictions stated in the stock certificates or in "buy and sell" agreements among the shareholders which are designed to prevent strangers from becoming stockholders or obtaining management control. These agreements also specify the price at which the other shareholders or the corporation may repurchase the stock of a shareholder. This price may be fixed in amount, determined by a formula, book value, or arrived at in some other manner which may yield a price substantially more or less than fair market value. However, under the proposed regulation, transferability is keyed only to "fair market value" even if there is a "buy and sell" arrangement among the associates.

The test for transferability of interests is stated as the power of substitution. "In order for this power of substitution to exist in the corporate sense, the member must be able, without the consent of other members, to confer upon his substitute all the attributes of his position in the organization." An executive who is also a shareholder in a corporation does not ordinarily have the power to transfer his right to employment by the corporation to the purchaser of his stock. Yet, if the language of the proposed regulation is taken literally, an associate in an association would have the right to confer this "attribute" of his position in the organization upon his substitute. The right of "centralized management" to hire or discharge employees is one of the basic tests in determining whether centralized management exists and employment rights are not ordinarily incidental to corporate stock ownership.

Businessmen engaged in corporate enterprises are in no way required to permit an employee-shareholder to transfer his employment status to the transferee of his stock. It is inconceivable that it is the intention of this section of the proposed regulations that the transferability of employment should be required of professional men who choose to do business as an association. Doctors and other professional men differ in their specialization, competence, and experience. It would be most illogical and unreasonable to assume that a surgeon who is retiring as an associate of an association after a lifetime of service should be able to transfer employment rights to any physician of his choice including someone who may be qualified in a specialty other than surgery.

In terms of practical reality, the persons engaged in the practice of medicine and the other learned professions derive their professional income essentially from personal services and not invested capital. Medical clinics doing business as associations generally lease their offices from building corporations which they may or may not control. Even the equipment used by the clinic may be leased. Consequently, the value of each associate's interest in the physical assets of the clinic is most often inconsequential and incidental. As recognized in Example (1), except upon complete liquidation, it is generally provided that no member has any interest in assets. Therefore, the interest which a member may have in the assets of a clinic doing business as an association is *de minimis* and not subject to a fair market value determination. Any payment made by a clinic to a retiring associate for his interest is either of a token nature or arbitrarily determined without any consideration being given to so-called fair market value.

After the payment of salaries to associates and other employees, rent and other items of overhead, any income remaining is generally distributable in proportion to salaries and constitutes added compensation for services rather than dividends. Consequently, clinics as well as personal service corporations customarily may have little or no income available for dividends after payment of reasonable salaries.

In our opinion, there is no judicial or statutory precedent in the Federal tax law for the following provision:

> Furthermore, although the agreement provides for the transfer of a member's interest, there is no power of substitution and no transferability of interest if under local law

Provision for continuity of life is admittedly a fundamental characteristic of both associations and corporations. Likewise, it is a common characteristic among partnerships and was so recognized by Congress in the enactment of Section 708. Although continuity of life is a characteristic essential to the existence of an association, it is *not* a distinguishing characteristic between associations and partnerships. Accordingly, it is our opinion that this standard should be stated in the regulations so as to provide that if the underlying agreement establishing an association does not permit continuity of life, the absence of this factor is significant in determining whether the organization is or is not an association.

Centralization of Management

Under the 1939 Code, Section 19.3797–2, Regs. 103, provided that an association

> . . . includes an organization, created for the transaction of designated affairs, or the attainment of some object, which, like a corporation, continues notwithstanding that its members or participants change, and the affairs of which, like corporate affairs, are conducted by a single individual, a committee, a board, or some other group, *acting in a representative capacity*. (Italics supplied.)

Section 301.7701–2 (c) of the proposed regulations provides that an organization has centralized management if any person or group of persons has continuing exclusive authority to make management decisions. The qualification that these persons must be "acting in a representative capacity," which was an essential element in the prior regulations, has been deleted. The centralized management which is characteristic of the typical association or corporation is derived from the process of representation. The persons who serve on a corporate board of directors or the board of an association function both as *management* and as *representatives* of the shareholders or associates.

Centralized management in itself is an insufficient standard and is an element traditionally characteristic of partnerships. Partnership agreements among doctors, lawyers, and other professional men commonly provide for centralized management in the senior partners, or in managing partners, or in the partner or partners who have a controlling interest in ratio of profits. Unless qualified by appropriate language, "centralized management" does not provide a clearly distinguishing characteristic between associations and partnerships.

The proposed regulation states:

> Usually, the act of any partner within the scope of the partnership business binds all the partners; and even if the partners agree among themselves that the powers of management shall be exclusively in a selected few, this agreement will be ineffective as against an outsider who had no notice of it.

If this language is intended to be applicable in determining whether the centralized management characteristic of an association exists, then it is in our opinion inconsistent with Section 7701 (a) (3) of the 1954 Code which states that the term "corporation" includes associations.

Under prevailing state law, an outsider dealing with an associate who is a member of an association but not of its governing board will have the same status as if he were dealing with a member of a partnership who has limited authority under the partnership agreement. The situation is further complicated from a legal standpoint because an associate as an employee of an association and a junior partner in a partnership are both clothed with apparent authority and an outsider without notice as to the limited authority of these persons will generally be protected under local law. Under the test of centralized management cited above, no association could qualify under the regulation as an association for tax purposes even though the Code itself specifically includes associations by name in the corporate tax classification.

As reported in the *Galt* and *Kintner* cases, centralized management in a medical clinic doing business as an association involves such matters as controlling hours of work, vacations, travel, salaries, conflicts which arise among associates and other employees, complaints against doctors, purchase of equipment, hiring or discharging employees and doctors, etc. These are essentially internal matters which only incidentally involve outsiders.

Limited Liability

Attributes of the corporate form of organization, which are not generally attainable by associations, should not be established as tests or standards in determining what is to be included under the term "association." Common law associations do not ordinarily qualify as separate persons or entities. Since the Code expressly includes "associations" in the corporate classification, the creation of a separate personality or entity is not material in the determination of corporation status for tax purposes. If the separate personality, not ordinarily attainable by associations, is of no consequence in the classification, then those corporate characteristics that depend upon the creation of an artificial personality are likewise inconsequential.

The capacity to contract debts for which other persons (including the associates) are not personally liable, is generally recognized as unattainable by common law associations. In this regard an association resembles a partnership, but Congress disregarded this resemblance in the statutory classification of business mediums; and it, therefore, should be disregarded in the proposed regulations. In our opinion, it is contrary to the clear intent of the statute to use "limited liability" as a standard or test in determining whether a particular organization is an association or partnership for tax purposes.

The *Morrissey* case, cited in the proposed regulations, acknowledges that both the trust and the corporation permit "the limitation of the personal liability of participants to the property embarked in the undertaking." The case involved a trust which the Court determined should be treated as a

MEDICAL NEWS

CALIFORNIA

Dr. Dimond to Head Institute at Scripps Clinic.—Dr. Edmunds Grey Dimond, chairman, department of medicine, and director, Cardiovascular Laboratory, University of Kansas Medical Center, Kansas City, will become the first director of the new Heart-Lung Institute and head, division of cardiology, Scripps Clinic and Research Foundation, La Jolla, on July 1. The institute provides Dr. Dimond and his group with 5,000 net square feet of laboratory space and facilities for patient care and postdoctoral education. Dr. Dimond will enlarge his present fellowship training program in cardiology at the new institute.

Personal.—Dr. Joseph D. Teicher, Beverly Hills, Child Guidance Clinic of Los Angeles, was appointed adjunct professor of child psychiatry, University of Southern California School of Medicine, and director of the Children's Psychiatric Services, Los Angeles County General Hospital, effective July 1.——At the third annual meeting of the Western Pharmacology Society, Dr. Howard R. Bierman, clinical professor of medicine, College of Medical Evangelists, Loma Linda and Los Angeles, was inducted as the president for the 1960-1961 term.——Dr. Thomas H. Brem, chairman, department of medicine, University of Southern California, Los Angeles, was appointed editor-in-chief of the Audio-Digest Foundation, according to Dr. Donald D. Lum, Alameda, president of the California Medical Association's nonprofit subsidiary. Dr. Brem succeeds Dr. Edward C. Rosenow Jr., who recently resigned to become executive director of the American College of Physicians, Philadelphia.

FLORIDA

Report from Poison Control Centers.—The J. Hillis Miller Health Center of the College of Pharmacy, University of Florida, Gainesville, in its bulletin of the Bureau of Professional Relations reported that a total of 1,122 poisoning cases were reported to the 15 state-wide poison control centers between July 1 and Dec. 31, 1959. The highest number of cases, 259, was reported at the Jacksonville station, with 251 cases reported at the Miami center. The following agents were involved in the poisoning cases (including the state totals for each agent): internal medication (514); insecticides (134); cleansing and polishing agent (128); petroleum, including kerosene (89); external medication (57); and poisonous plants (56). Of the total cases for the state, 486 involved white males and 461 white females. Two-hundred-thirty cases involved children 1 year of age, 272 cases involved children 2 years old, and there were 149 cases of poisoning in 3-year-olds. In 255 cases the age was 20 and over.

HAWAII

Annual Meeting in Hawaii.—The Hawaii Medical Association will hold its 104th annual meeting in Honolulu May 12-15. The scientific program includes the following panel discussions and moderators:

Medico-Socio-Economic Aspects of the Aged, Dr. Fred I. Gilbert Jr., Honolulu.
The Stroke Syndrome, Dr. Abe B. Baker, Minneapolis.
The Elderly Diabetic, Dr. Peter H. Forsham, San Francisco.
Hypertension, Dr. Fred T. Darvill Jr., Mt. Vernon, Wash.
Peripheral Vascular Disease, Dr. Darvill.
Management of Heart Failure, Dr. Forsham.

Dr. Toru Nishigaya, Honolulu, will present the presidential address the evening of May 13. Scientific and technical exhibits and a program of ladies' activities are arranged. Entertainment includes the annual golf tournament. For information, write Lee McCaslin, 510 S. Beretania St., Honolulu, Hawaii, Secretary.

IOWA

State Meeting in Des Moines.—The Iowa State Medical Society, which was organized in 1860, will hold its annual meeting April 24-27 at the Veterans Memorial Auditorium, Des Moines, under the presidency of Dr. John W. Billingsley, Newton. Symposiums are planned on "Ankle Injuries" and "Modern Concepts in Coronary Artery Disease—Their Practical Applications." The Arthur Erskine Memorial Lecture, "The Visualization of the Vascular System," will be given by Dr. Hillier L. Baker Jr., Rochester, Minn., the morning of April 26. A special address will be given the morning of April 27 by Dr. Leonard W. Larson, Bismarck, N. D., chairman, Board of Trustees, American Medical Association. The program includes the following papers by out-of-state speakers:

Frequency and Nature of Athletic Injuries, Dr. Thomas B. Quigley, Boston.
Sports for Children, Dr. Robert A. McGuigan, Winnetka, Ill.
Prevention and Treatment of Injuries in Football in the Boston High Schools, Dr. Joseph H. Burnett, Boston.
Management of Ankle Injuries Sustained in Sports, Dr.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

a transfer of a member's interest results in the dissolution of the old organization and the formation of a new organization.

The fact that under a technical interpretation of the laws of a particular state a "new" organization may be created everytime a member of a large clinic is added or a member dies or withdraws is irrelevant for tax purposes. Furthermore, the status of the law in most states is uncertain or unknown as to whether the death or withdrawal of a member of an association engaged in a business activity causes a technical dissolution even when the business continues without interruption. The provision cited above is grossly unfair and constitutes an artificial standard to taxpayers and one which could not be administered equitably by Internal Revenue personnel.

Transferability of interests is implied in the characteristic of continuity of life. Without it the actual operation of a business cannot continue after the death or withdrawal of a member. In this regard, we call attention to the fact that transferability of interest was not a criterion in Section 19.3797–2, Regs. 103, under the 1939 Code, and its absence in no way impaired the ability of the courts to determine the tax classification of business organizations in cases decided with reference to this regulation.

Recommendation

The American Medical Association recommends modification of the provisions and examples contained in the proposed regulations in accordance with the comments and suggestions herewith submitted.

Respectfully submitted
AMERICAN MEDICAL ASSOCIATION
F. J. L. Blasingame, M.D.
Executive Vice-President

NEW LEAFLET ON A. M. A. SERVICES

The A. M. A. is expanding its services to the public and the profession in the 1960's. This is the message set forth in a new leaflet entitled "A. M. A. Looks Ahead to Better Health," which is being distributed to physicians with their 1960 membership cards.

The leaflet outlines some of the major challenges facing medicine in the new decade and points out a few of the principal areas of activity undertaken by the Association in the interests of the medical profession and the public. In addition, the leaflet urges physicians to use their membership privileges for the benefit of themselves and their patients.

CHANGE OF DATE OF CONGRESS ON INDUSTRIAL HEALTH

The Council on Occupational Health, formerly the Council on Industrial Health, reports that its annual Congress on Industrial Health has been postponed to the autumn of this year because of the inclement weather frequently encountered in February. The 20th annual Congress on Industrial Health will be held on Oct. 10-12, 1960, at the Hotel Charlotte in Charlotte, N. C.

MEDICAL FILM REVIEWS AVAILABLE

The 11th annual publication of Reviews of Medical Motion Pictures is now available on request from the Film Library of the American Medical Association. This publication is prepared by the Division of Communications, Department of Medical Motion Pictures and Television, and contains reprints of all reviews published in The Journal of the American Medical Association during 1959.

VITAL STATISTICS IN THE 15TH CENTURY

The Orejones of Cuzco who supplied me with information are in agreement that in olden times, in the days of the Lord-Incas, all the villages and provinces of Peru were notified that a report should be given to the rulers and their representatives each year of the men and women who had died, and all who had been born, for this was necessary for the levying of the tributes as well as to know how many were available for war and those who could assume the defense of the villages. This was an easy matter, for each province at the end of the year had a list by the knots of the quipus of all the people who had died there during the year, as well as of those who had been born. At the beginning of the new year they came to Cuzco, bringing their quipus, which told how many births there had been during the year, and how many deaths. This was reported with all truth and accuracy, without any fraud or deceit. In this way the Inca and the governors knew which of the Indians were poor, the women who had been widowed, whether they were able to pay their taxes, and how many men they could count on in the event of war, and many other things they considered highly important.—The Incas of Pedro de Cieza de Leon, translated by H. de Onis, edited by V. W. von Hagen, Norman, University of Oklahoma Press, 1959, page 177.

CHANGE OF ADDRESS

If you change your address please notify The Journal at least six weeks before the change is made. Include the address label clipped from your latest copy of The Journal, being sure to clearly state both your old and new address. If your city has Postal Zone Numbers, be sure to include this Zone Number in your new address.

A banquet is planned for the evening, with Dr. Stephen W. Preston, Missoula, serving as toastmaster. Guest speaker at the meeting will be Dr. Irwin H. Kaiser, head, department of obstetrics and gynecology, University of Utah College of Medicine, Salt Lake City, who will present "Carcinoma of the Cervix."

NEBRASKA

State Meeting in Lincoln.—The 92nd annual session of the Nebraska State Medical Association will be held April 25-28, at the Hotel Cornhusker, Lincoln, under the presidency of Dr. Ezra E. Koebbe, Columbus. The House of Delegates and Board of Councilors will conduct daily meetings. The scientific session will open on Tuesday, April 26, and continue through Thursday noon with presentations by physicians from all parts of the country. At the annual banquet on Wednesday evening the association will recognize its 50-year practitioners who will be honored guests. A musical revue by six physicians from the Greene County Medical Society of Springfield, Mo., will be presented for the banquet attendants, labeled, "Your Medical Hit Parade." Thirty-four technical exhibits are scheduled. A program on "Space Medicine" will be presented on Thursday morning and the session will close at noon. For information, write Mr. M. C. Smith, 1315 Sharp Bldg., Lincoln, Neb., Executive Secretary.

NEW HAMPSHIRE

Campaign for Dartmouth Expansion.—Dartmouth Medical School, Hanover, announced the opening of its drive for 10 million dollars in capital funds. About 5 million dollars of the total sought to expand the teaching and research facilities has already been subscribed through major gifts from foundations and the U. S. Public Health Service. Among principal objectives of the fund campaign are: (1) construction of a new 3-million-dollar seven-story Medical Science Building, now under way; (2) construction of library and auditorium facilities; and (3) increasing endowment to place the expanded faculty on a permanent basis. The Dartmouth Medical School offers a basic medical-science program for the first two years of medical education.

NEW YORK

Director of Environmental Sanitation Appointed.—The permanent appointment of Meredith H. Thompson, Dr. Engr., of Troy, as director of the Bureau of Environmental Sanitation of the State Health Department was announced. Dr. Thompson, who has been serving as acting director of the Bureau of Environmental Sanitation since September, 1958, joined the State Health Department in 1938 as junior sanitary engineer in the bureau. In 1947, Dr. Thompson was appointed director of environmental hygiene for the Rensselaer County Health Department, and in 1951, was appointed training section chief, bureau of environmental sanitation. He was named assistant director of the bureau in 1955.

Approve Closure of Tuberculosis Hospital.—The approval of closure of the Broome County Tuberculosis Hospital at Chenango Bridge, effective March 31, was announced by Dr. Herman E. Hilleboe, State Health Commissioner. The hospital, open since 1931, has been operated for the care of tuberculosis patients in Broome County. The announcement by Commissioner Hilleboe followed approval of an application from the Broome County Board of Supervisors to close the hospital. The hospital has a 96-bed capacity. Tuberculosis hospital care for residents of the county will be provided by the Homer Folks Tuberculosis Hospital at Oneonta. Chest clinic services in Broome County will be continued under county auspices.

Annual Conference on Health.—The 56th Annual Health Conference will be held May 23-26 at the Hotel New Yorker, New York City. The first general session, May 24, will include as speakers New York Governor Nelson A. Rockefeller; Dr. Norman S. Moore, Ithaca, president-elect, Medical Society of the State of New York; and Dr. Herman E. Hilleboe, State Health Commissioner. A second general session will be held at 10 a. m., May 25. Section meetings are planned, to include the following discussions: use of antibiotics, experience with oral polio vaccine, importance of diet in heart disease, psychiatric problems of school children, rehabilitation, community planning for improved environment, prepayment of hospital care, and the growing importance of virology. The conference, called each year by the New York State Health Commissioner, is sponsored by Annual Health Conference, Inc., a nonprofit organization chartered by the secretary of state.

Hospital News.—Dr. Jameson L. Chassin was appointed director of the department of surgery at Booth Memorial Hospital, a 200-bed general hospital in Flushing, L. I., operated by the Salvation Army. Dr. Chassin is instructor in surgery at New York University College of Medicine and is on the attending staff of University and Bellevue hospitals.——Dr. Harold P. Curran, Great Neck, was named director of radiology at St. Clare's Hospital, Schenectady. Prior to coming to St. Claire's Hospital Dr. Curran was associate radiologist at St. Peter's General Hospital, New Brunswick, N. J. Dr. Moses Sommer, director of radiology at St. Clare's for four years, resigned to go into private practice. ——The president of the board of directors of St. Claire's Hospital, Schenectady, appointed Dr.

Thomas B. Quigley, Boston.
Heart Disease in Pregnancy, Dr. Roy C. Holly, Omaha.

Specialty groups will meet April 25. The president's reception and annual banquet is planned for the evening of April 26. Entertainment includes a golf tournament. For information, write Mr. Donald L. Taylor, 529 36th St., Des Moines 12, Iowa, Executive Director.

MASSACHUSETTS

Foreign Visitor.—Dr. Albert Neuberger, professor of chemical pathology, St. Mary's Hospital Medical School, London, England, was visiting physician-in-chief pro tempore at the Peter Bent Brigham Hospital for the week of March 13th through March 19th. He gave the E. Stanley Emery Jr. Memorial Lecture, sponsored by the department of medicine, entitled "Recent Work on the Absorption of Protein in Normal Man and in Patients with Steatorrhoea."

Dr. Granger Goes to Afghanistan.—Dr. George B. Granger, of East Northfield, recently flew to Kabul, Afghanistan, accompanied by his wife, where he will spend about two years. Dr. Granger retired in 1953 as chief of obstetrics and gynecology at Nassau Hospital in Mineola, L. I., New York, and had a private practice in Rockville Center from 1926 to 1953. In Afghanistan the government will provide a place to live, subsistence, and necessary transportation. The Medical International Cooperation organization will send medical equipment and drugs and will pay the fare to and from the field.

Summer Course in Research Methods.—The third biannual course, "Modern Research Methods in Biology and Medicine," is to be held July 5-15 at the Massachusetts Institute of Technology, Cambridge. Material will be presented in the form of "Instrumentation Elements." Knowledge of higher mathematics is not a prerequisite for the course. The 1960 program will be under the direction of Prof. Kurt S. Lion, associate professor of applied biophysics. Lectures will be given by specialists from M. I. T. and other universities. All facilities at M. I. T. will be open to the members of this course, and housing will be available in the institute's dormitories. Application forms and information may be obtained from Dr. James M. Austin, Director of the Summer Session, Room 7-103, Massachusetts Institute of Technology, Cambridge 30, Mass.

MISSOURI

Annual Lecture.—The Thompson, Brumm & Knepper Clinic, St. Joseph, announced that the 11th annual Dr. F. G. Thompson Sr. Memorial Lecture will be held on Thursday, May 19, 8:15 p. m. in the Clinic Building, 902 Edmond St., St. Joseph. The speaker will be Dr. Leonard F. Jourdanais, associate professor of medicine, Northwestern University School of Medicine, and chairman of the department of medicine at the Evanston General Hospital, Evanston, Ill. The subject will be "Chronic Ulcerative Colitis: An Enigma."

Day Camps for Retarded Children.—The St. Louis Association for Retarded Children, 6376 Clayton Road, is accepting camp applications from parents of retarded children 14 years and older for attendance at its residence camp, Sherwood Forest, Cuivre River State Park near Troy. Attendance is limited to one week. Applications also are being accepted for attendance of mentally retarded children 9 years and older at the association's nine-week day camp, June 20-Aug. 10, at Tower Grove Park. The number of children taken into the program will b determined by available funds.

Symposium on Food Additives.—A Nutrition Symposium sponsored by the University of Missou School of Medicine, Columbia, to be held in th Medical Auditorium Center April 27 will be e titled "Additives and Residues in Human Foods Dean Vernon E. Wilson, of the school of medicine, will open the meeting with welcoming remarks. The following topics are planned:

Additives and Residues in Foods of Animal Origin.
Additives and Residues in Foods of Plant Origin.
Manufacturer Viewpoint of Additives and Residues.
Government View of Additives and Residues.
Medical View of Additives and Residues.

A panel discussion on collected questions on the presented topics is planned for the afternoon, moderated by Dr. Robert L. Jackson, Columbia, professor of pediatrics. For information, write Prof. T. D. Luckey, Chairman of Biochemistry, School of Medicine, University of Missouri Medical Center, Columbia, Mo.

MONTANA

Meeting of Obstetricians and Gynecologists.—The 14th annual session of the Montana Obstetrical and Gynecological Society will be held Saturday, May 7, at the Florence Hotel, Missoula. Dr. Richard L. Peterson, Hamilton, president of the society will open the program with welcoming remarks. The following papers are scheduled on the program:

Polyhydramnios with Subsequent Complications of Baby, Dr. Albert L. Vadheim Jr., Bozeman.
A Study of Cervical Conization with Five or More Years Follow-up, Dr. Robert E. Asmussen, Great Falls.
Pseudohermaphroditism, Drs. Matthew W. Calvert, Laurel, and Robert E. Hulit, Billings.
Obstetrical Analgesia and Anesthesia and Fetal Embarrassment, Dr. Irwin H. Kaiser, Salt Lake City.
Pitfalls with Pit, Dr. Robert C. Whitesitt, Helena.
Maternal Mortality in Montana: A Five Year Study, Drs. Robert J. Casey, Great Falls, and David P. Findley, Helena.
Roentgen Pelvimetry, Dr. Eugene J. P. Drouillard, Missoula.

the university faculty until Aug. 31, 1961, but is relinquishing the deanship on July 1 of this year to provide for a "smooth transfer" of administrative duties to his successor. Dr. Davison will serve during the 1960-1961 academic year as James B. Duke Professor of Pediatrics, a job which he has held for many years in addition to the deanship. Dr. Woodhall is a national consultant in neurosurgery to the Veterans Administration and is vice-chairman of the Special Medical Advisory Group to the administrator of the Veterans Administration. He is serving as treasurer for the second International Congress of Neurological Surgery to be held in this country next year. He is a member of the executive council of the World Federation of Neurosurgical Societies, a member of the board of governors, American College of Surgeons, and in 1944 was president of the American Academy of Neurological Surgeons.

PENNSYLVANIA

Open New Radiology Facilities.—Presbyterian Hospital and the University of Pittsburgh announced the opening of joint radiology facilities in the wing connecting the hospital and the university's School of the Health Professions building. The new facilities will serve Presbyterian Hospital, Woman's Hospital, Eye and Ear Hospital, and the University of Pittsburgh. Cost of the new area is about one million dollars, including more than $300,000 for new equipment. The radiology department occupies about 16,000 square feet, which doubles the space that had been used for x-ray purposes at Presbyterian Hospital. Diagnostic x-ray work is being done in 12 separate units on the third floor, and x-ray therapy and isotope facilities are being utilized on the fourth floor, where space for laboratory research is provided. It is planned to convert the areas formerly used for radiologic purposes into patient rooms.

Philadelphia

Dr. Cantarow Honored.—Dr. Abraham Cantarow, professor of biochemistry, Jefferson Medical College, was honored March 30 when an oil protrait of him was designated for permanent display at the college among the memorable faculty members. The portrait was commissioned by the senior class. Dr. Benjamin F. Haskell, clinical professor of proctology, made the presentation speech, and Dr. William A. Sodeman, dean, accepted the portrait for the institution.

Surgery Board Certifies Nun.—The *New York Times* of Feb. 14 reported that Sister Mary Ligouri, M.D., of the Sisters of Mercy in suburban Merion, has become the first member of the Roman Catholic Order of Nuns to be certified by the American Board of Surgery. Sister Mary Ligouri is awaiting assignment to India, where other members of the Sisters of Mercy staff the Dalal Memorial Hospital in Jamshedpur. She is now stationed at Misericordia Hospital.

Program of Construction for Hahnemann.—Hahnemann Medical College and Hospital announced a 10-year, 15-million-dollar program of construction designed to provide, in the first phase of the plan, a clinical research building, a surgical pavilion, and a student nurses' residence and classroom building. Eight major buildings covering medical education, medical research, and patient care are contemplated, according to Mr. Watson Malone III, president of the 112-year-old institution's board of trustees. The over-all plan also calls for a new medical college building, a resident and intern residence, an outpatient clinic, patient pavilion, and other related buildings. The plan calls for the razing of all Hahnemann buildings except the present hospital structure on Broad Street, built in 1928, and the Klahr Building fronting on Fifteenth Street, constructed in 1938. The buildings to be torn down were all built previous to 1890. Construction of the Clinical Research Building, to cost $1,700,000, will enable Hahnemann Medical College to combine the more than 97 major research projects currently underway into a single, specially designed facility. More than $1,200,000 is spent annually on medical research at Hahnemann. The federal government has granted the institution $882,000 in matching funds for the construction of the research building. The surgical pavilion will cost an estimated $400,000. The new nurses' residence and classroom building, to cost about $1,500,000, will replace the present structures built in 1888. Total cost for the first phase of construction has been estimated at $3,600,000. The building plans call for the construction of two floors of parking under all of the new structures. Construction is expected to begin during June.

TENNESSEE

Dr. Alden Named Acting Dean.—Roland H. Alden, Ph.D., who became associate dean of the Graduate School—Medical Sciences at the University of Tennessee Medical Units, Memphis, Jan. 1, was named acting dean of the university's School of Biological Sciences, effective July 1. Dr. Alden will retain his position as professor and chief of the division of anatomy. He succeeds Thomas P. Nash Jr., Ph.D., who is retiring this summer. Dr. Nash has served as dean of the school since it was organized in 1928. The School of Biological Sciences consists of the divisions of anatomy, chemistry, pathology and microbiology, pharmacology, and physiology. Dr. Alden has been a member of the university staff since 1942.

Thomas H. Mason to the medical board. Dr. Mason was appointed chief of the newly formed neurosurgery department at the directors board meeting held at the hospital Dec. 7.

New York City

Annual Conference on Tuberculosis.—The annual conference of the New York Tuberculosis and Health Association will be held Tuesday, April 26, starting at 10 a. m., at the Hotel Statler Hilton. Airborne infection and the prospects of its control will be discussed by Dr. Richard L. Riley, Baltimore. Dr. James J. W. Raleigh, Washington, D. C., will speak on the patient with the open cavity in the lung whose sputum is free of tuberculosis germs. The use of Isoniazid in treating and preventing tuberculosis in children will be outlined by Dr. Edith H. M. Lincoln, New York City. Discussion periods will follow the presentation of each paper. Dr. Clara Regina Gross, associate professor of clinical medicine, College of Physicians and Surgeons, Columbia University, will moderate the conference.

Lectures on Mental Health and Human Relations.—The integration of mental health concepts with the theory and practice of the human relations professions is the subject of a lecture program sponsored by the Bank Street College of Education as a memorial tribute to the late Dr. Ruth Kotinsky, psychological researcher. The lectures will be given at the Carnegie Endowment International Center, 345 E. 46th St., beginning April 23, when Dr. Jules V. Coleman, clinical professor of psychiatry, Yale University School of Medicine, New Haven, Conn., will speak on the general subject of medicine. Religion and law will be discussed May 21 by Dr. Earl A. Loomis Jr., professor of psychiatry and religion, Union Theological Seminary, New York City, and Mr. Fowler V. Harper, Simeon E. Baldwin Professor of Law, Yale University. On Nov. 19, psychology and community psychiatry will be discussed by Dr. Viola W. Bernard, director, division of community psychiatry, Columbia University College of Physicians and Surgeons, and Miss Sibylle V. Escalona, professor of psychology, Albert Einstein College of Medicine, Yeshvia University. Admission is free, and information may be obtained from the Bank Street College of Education, 69 Bank St., New York 14.

Passano Award Given to Dr. Dubos.—The board of directors of the Passano Foundation announced that Rene J. Dubos, Ph.D., Rockefeller Institute, New York City, was selected as the recipient of the $5,000 Passano Award for 1960. On Wednesday evening, June 15, during the convention of the American Medical Association in Miami Beach, a reception and dinner will be held at the Americana Hotel to honor Dr. Dubos. Dr. E. Vincent Askey, Los Angeles, at that time to be President of the A. M. A., will speak on the place of fundamental research in the practice of medicine. Professor Emeritus Selman A. Waksman, of Rutgers University, New Brunswick, N. J., will make an appraisal of Dr. Dubos's role in the development of modern science. The presentation of the award to Dr. Dubos is "a recognition of his many and fruitful researches in bacteriology and biochemistry, notably the use of specific enzymes in biochemistry, the chemotherapy of tuberculosis, and pioneer work on antibiotics from soil organisms." The Passano Foundation was formed late in 1943, having as its sole purpose the encouragement of medical science and research, particularly that having a clinical application. It is sustained by annual contributions from The Williams and Wilkins Company, publishers of medical and scientific books.

Three Physicians Honored for Service.—Three awards of distinction for "outstanding service to medicine" were presented March 30 by the State University of New York Downstate Medical Center, Brooklyn, at a convocation celebrating the centennial anniversary of medical education in Brooklyn. The awards went to Dr. Jean Redman Oliver, distinguished service professor of pathology of the state university; Dr. John J. Masterson, president of the board of trustees of the Kings County Medical Society; and Dr. Frank L. Babbott, former president and trustee of the Long Island College of Medicine, the predecessor institution of the Downstate Medical Center. Dr. Oliver, now of Chatham, N. J., served as chairman of the department of pathology at the Downstate Medical Center and its predecessors, the college division of the Long Island College Hospital and the Long Island College of Medicine, from 1929 to 1954. Dr. Masterson has been trustee of the Medical Society of the State of New York for over 10 years. A director of the Catholic Medical Mission Board and a past-president of the Brooklyn Catholic Physician's Guild, Dr. Masterson was last year named "Catholic Physician of the Year" by the National Federation of Catholic Physicians Guilds. Dr. Babbott, appointed to the faculty of the department of pediatrics of the Long Island College Hospital in 1924, became assistant dean of the college in 1927 and became the first president of the reorganized Long Island College of Medicine in 1931.

NORTH CAROLINA

Dr. Woodhall Named Medical School Dean.—Dr. Barnes Woodhall, a veteran of 23 years on the faculty at the Duke School of Medicine, Durham, will succeed the school's first dean, Dr. Wilburt C. Davison, who is retiring after 33 years in that position. Dr. Davison will not officially retire from ıs elected secretary. The 1961 annual meeting ll be held at the Hotel Statler-Hilton, New York ty, March 23-25. Executive Secretary is Marion F. ınger, Ph.D.; headquarters are at 1790 Broadway, w York City.—Dr. Louis J. Feit, New York ty, is the president-elect of the American Otorhilogic Society for Plastic Surgery. The society's esident is Dr. Thomas E. Briant, of Welland, ıtario, Canada. Dr. Joseph G. Gilbert, of Roslyn ights, N. Y., was reelected secretary.

ctology Meetings.—The 59th annual meeting of American Proctologic Society will be held ril 25-27 at the Shamrock Hilton Hotel, Houston, xas. The scientific sessions, open to all members the medical profession, include the following nposiums: "Parasitic Lesions of Colon and orectum," "Large Bowel Preparation," and ıthological Significance of Polyps of the Colon l Rectum." Two sessions of postgraduate dission courses are planned for the afternoon of ril 25. Panel discussions and exhibits are nned, and the annual banquet will be held ril 27, 7:00 p. m. On April 29-May 1, the society l meet with the Mexican Proctologic Society in xico City at the Continental Hilton Hotel, with following symposiums scheduled for the scien sections: "Amebiasis and Colitis," "Anorectal gery," and "Tumors." Panel discussions and ibits as well as tours are also planned for the xico City meeting. A program of ladies' activi is planned for the Houston and Mexico City sions. For information, write Dr. Norman D. gro, 10 Peterboro, Detroit 1, Secretary.

ninar Cruise to Baltic Area.—The Duke Univer Medical School will sponsor its fifth postgradu medical seminar cruise in June, Dr. William M. holson, assistant dean in charge of postgraduate ıcation, announced. Designed to enable physins to "combine postgraduate study with overs vacations," the cruises feature shipboard inıction by members of the Duke Medical School ulty. This year's cruise will be to the Baltic a. Sailing from Wilmington, Del., on June 5 l from New York City on June 8 aboard the ise ship "Ariadne," the physicians will visit cities t include Leningrad, Helsinki, Stockholm, penhagen, and Hamburg. The cruise will termie at Hamburg, Germany, June 28. Shipboard tures will be given on subjects in medicine, liatrics, and thoracic surgery. The instructional gram will provide credit toward postgraduate uirements of the American Academy of General ıctice. Plans are being made for visits to medi centers in Leningrad, Helsinki, Copenhagen, l Stockholm. Information can be obtained by iting to the director of Postgraduate Education, ıke University Medical School, Durham, N. C.

FOREIGN

Course in Rhinoplasty in Israel.—An international course, "Reconstructive Surgery of the Nasal Septum and External Pyramid," will be given at Hebrew University, Hadassah Medical School in Jerusalem, Israel, July 24-Aug. 6, 1961. This will follow the International Congress of Otorhinolaryngology to be held in Paris earlier in July, 1961. The course will be sponsored by the American Rhinologic Society and will be under the direction of Dr. Maurice H. Cottle, professor of otorhinolaryngology, Chicago Medical School. The course will offer the same basic program as has been given in the United States, consisting of lectures, surgical demonstrations, scientific exhibits, seminars, laboratory material, and studies. The faculty will consist of rhinologists from the United States, Mexico, Israel, and Australia. Early application for membership is suggested. For information, write Dr. Robert M. Hansen, 1735 N. Wheeler Ave., Portland 17, Ore., or Dr. Zvi Rosen, 16 Nathan Straus St., Jerusalem, Israel.

Symposium on Cybernetic Medicine.—The first International Symposium of Cybernetic Medicine, organized by the International Society of Cybernetic Medicine, will be held in Naples, Italy, Oct. 2-4, under the presidency of Prof. Aldo Masturzo, of Naples University. The general theme will be "The Introduction of Cybernetic Methods in Modern Medicine." Official speakers will include Prof. Norbert Wiener, director, department of mathematics, Massachusetts Institute of Technology, Cambridge, Mass.; Prof. Paul Nayrac, director, neuropsychiatric department, University of Lille; Prof. S. T. Bok, director, Institute of Brain Research, University of Amsterdam; Dr. Giuseppe Foddis, Naples; Prof. Minoru Kono, director, Institute of Medical Research, Tokyo. Receptions, trips to Pompei, Sorrento, and other points of interest near Naples, panel discussions, and exhibits of cybernetic machines of medical interest are being organized. Those wishing to participate should send, before June 30, the registration fee ($10) and titles of papers to Prof. Renato Vinciguerra, Secretary, S. I. M. C. Via Roma, 348, Naples, Italy.

Colon and Rectal Symposium at Bologna, Italy.—The Colon and Rectal Section of the International College of Surgeons will hold a symposium on diseases of the colon and rectum at the University of Bologna, Italy, May 20-21, under the direction of Prof. G. Gherardo Forni, professor emeritus of surgery and dean of the university, and Prof. G. Placitelli, director, Clinica Chirurgica of the university. A panel discussion, "Congenital Malformations of the Anorectal Area (a) Embryology and Anatomy, (b) Pathology, and (c) Surgical Therapy and Results," is planned. Papers by invited authors from the U. S. are as follows:

TEXAS

Radium Society Honors Dr. MacComb.—Dr. William S. MacComb, Houston, received the Janeway Medal of the American Radium Society in ceremonies highlighting the 42nd annual meeting of medical organization in San Juan, P. R. Dr. MacComb presented the society's annual Janeway Lecture which memorializes pioneer contributions in radiation therapy by the late Dr. Henry Harrington Janeway. Lecturers each year are selected for "outstanding" scientific contributions.

Personal.—Dr. Robert T. E. Bishop, Dallas, was promoted to assistant medical director of Republic National Life Insurance Company. Since joining the company in October, 1958, Dr. Bishop has been associated with the medical and underwriting division.—Dr. Michael E. DeBakey, chairman of the department of surgery at Baylor University College of Medicine, Houston, gave the third annual John Alexander Lecture at the University of Michigan Medical Center, Ann Arbor, Nov. 12. The lectureship was established by the John Alexander Society in 1917 as a memorial to the former chief of thoracic surgery at the U-M. Dr. DeBakey's topic was "Surgery of the Aorta and Its Major Branches."

VERMONT

Establish Beecher Memorial Lecture.—The Vermont Heart Association, at its executive committee meeting on March 26 voted to establish a memorial lecture on some aspect of cardiovascular disease, on behalf of one of its past-presidents, Clarence H. Beecher, deceased. The first lecture will be given at the May clinical meeting of the Vermont Medical Society, to be held in Burlington May 12.

GENERAL

Conference on Health Education.—The 1960 Eastern States Health Education Conference of the New York Academy of Medicine will be held April 28-29, under the theme "The Dynamics of Education for Health," which will be given two lecture headings, "The Complex of Communication" and "The Expanding Dimensions of Public Health." At the dinner meeting April 28, Dr. John D. Porterfield III, deputy surgeon general, U. S. Public Health Service, will present "The Merchandising of Public Health." Registration fee is $15. For information, write Dr. Iago Galdston, 2 E. 103 St., New York 29.

Meeting of Pathologists and Bacteriologists.—The 57th annual meeting of the American Association of Pathologists and Bacteriologists will be held April 28-30 at the Hotel Peabody, Memphis, Tenn. A total of 60 papers are scheduled for presentation at the five scientific sessions, and 29 papers are scheduled to be read by title. A program of motion pictures and scientific exhibits are planned. The annual dinner ($8) is scheduled for 7 p. m., April 28. Registration fee is $3. The meeting will be preceeded by the 49th annual meeting of the International Academy of Pathology, April 25-27, at the Hotel Peabody, which will include a course, "Pathologic Physiology of the Adrenal Cortex." For information, write Dr. Russell L. Holman, Department of Pathology, Louisiana State University School of Medicine, New Orleans, Secretary.

Conference on Vascular Brain Disease.—On April 30-May 1, the International Conference on Vascular Disease of the Brain will be held at the Eden Roc Hotel, Miami Beach, Fla., in conjunction with the 12th annual meeting of the American Academy of Neurology. Conferences will consider experimental studies, diagnostic procedures, and therapy, and the following papers will be presented by foreign authors:

Use and Limitation of Angiography, Dr. James W. D. Bull, London, England.
EEG in Cerebral Vascular Disease, Dr. Henri Gastaut, Marseille, France.
Aneurysms, Dr. Lawrence S. Walsh, London, England.
Non-Aneurysmal Hemorrhage, Dr. Herbert H. Hyland, Toronto, Ontario, Canada.

Chairman of the conference committee is Dr. Richard P. Schmidt, Gainesville, Fla. The conference is supported by a grant from the National Institute of Neurological Diseases and Blindness, Bethesda, Md.

Psychoanalytic Meeting in Atlantic City.—The annual meeting of the American Psychoanalytic Association will be held May 6-9 at the Chalfonte-Haddon Hotel, Atlantic City, N. J. In addition to some 40 scientific papers and brief communications, there will be the following panels:

Learning Difficulties in Childhood.
The Psychoanalytic Theory of the Symbolic Process.
Problems in the Selection of Psychoanalytic Candidates.
Psychology of Twins.

The principal speech at the plenary session will be the presidential address, "The American Psychoanalytic Association, 1960," by Dr. Bernard Bandler, Boston. For information, write Mrs. Helen Fischer, Acting Executive Assistant, One East 57th St., New York 22.

Society News.—Dr. James E. Perkins of New York City, was installed as president of the National **Health Council** at its annual meeting March 17. Dr. James H. Sterner, medical director of Eastman Kodak Company, Rochester, N. Y., was named president-elect to succeed Dr. Perkins in 1961.—Dr. William S. Langford, of New York City, became president of the **American Orthopsychiatric Association**, Feb. 25. Fritz Redl, Ph.D., Detroit, was named president-elect, to take office in 1961. Dr. Gisela Konopka, Minneapolis, was elected vice-president, and Dr. Soll Goodman, Larchmont, N. Y.,

GOVERNMENT SERVICES

NAVY

Retirements.—Capt. Earl F. Evans, commanding officer of the U. S. Naval Hospital, Charleston, S. C., was retired after more than 29 years' service.—Capt. Verden E. Hockett was retired after completion of more than 20 years' service. At the time of his retirement he was serving as senior medical officer, U. S. Naval Station, Seattle, Wash.

VETERANS ADMINISTRATION

Personal.—Dr. Joseph S. Weltman, director of professional services at the Veterans Administration hospital in Lexington, Ky., was appointed manager of the VA Center in Togus, Maine.

PUBLIC HEALTH SERVICE

Mongolism. — "Mongolism — Hope Through Research," a newly published leaflet, tells of the broad research efforts underway at the National Institute of Neurological Diseases and Blindness to determine the cause and prevention of this disorder. Although the cause of mongolism is unknown, the condition is known to start before birth. A widely held theory has been that early in pregnancy some unknown factor interferes with the normal development of the embryo. According to a more recent theory reported in the pamphlet, the disorder may be triggered even before pregnancy. In the past year investigators found, in persons with mongolism who were studied, 47 chromosomes instead of the standard human 46.

To some researchers this new finding suggests that mongolism could begin with an irregularity in the human ovum before it is fertilized. Furthermore, only about one infant with mongolism per 1,000 births is born to a mother under 30 years of age. The rate rises with increasing age of mothers and reaches 2 or 3 per 100 births in women aged over 45 years. "Mongolism—Hope Through Research" is listed as Public Health Service Publication No. 720 and Health Information Series No. 94. Single free copies may be obtained from the National Institute of Neurological Diseases and Blindness, Bethesda 14, Md. Quantity orders cost $3.00 per 100 copies from the Superintendent of Documents, Government Printing Office, Washington 25, D. C.

Environmental Radiation.—A study is being initiated in San Juan County, New Mexico, in cooperation with the New Mexico State Department of Health, to determine the effects of environmental radiation on the health of large population groups. It will be extended later to other parts of the country. The site of the initial project is in one of the largest uranium-producing areas of the country. From earlier studies it has been determined that radioactivity from radium in the surface water of the Animas River has been higher than that found in most areas in the United States. Effective steps have been taken recently to reduce the amounts of radioactive waste discharge into the rivers in this area from milling operations, but the extensive data already obtained on radioactivity in the environment of this area present an unusually good opportunity to determine through further study the amounts of radioactivity that are currently being taken in by people, the amounts retained, the total "body burden," and the effects on health. Exhaustive study will also be made of the vital statistics of the area.

NATIONAL SCIENCE FOUNDATION

Russian Scientific Journals.—Much of the Soviet scientific periodical literature available in the United States today in the English language is in the form of cover-to-cover translations of Russian journals, with most of the translated editions matching the original issue for issue. The National Science Foundation has prepared in tabular form a list of 77 such journals (List of Russian Scientific Journals Available in English, February, 1960). The list includes nine medical titles, with the year translations were started, frequency of publication, agency through which journals may be subscribed to, sponsor, and subscription price.

OFFICE OF VOCATIONAL REHABILITATION

New Periodical.—*Rehabilitation Record*, a new bimonthly periodical prepared by the Office of Vocational Rehabilitation (OVR), made its appearance with the January-February, 1960, issue. The new publication will review activities of the federal-state program of vocational rehabilitation, with special emphasis on research developments supported by the OVR. Contributors to the first issue include Arthur S. Flemming, Secretary of Health, Education, and Welfare; Mary E. Switzer, director of the Office of Vocational Rehabilitation; the Reverend Thomas J. Carroll, director of the Catholic Guild for the Blind; and Dr. Frank H. Krusen, founder of the Mayo Clinic's department of physical medicine and special assistant to the OVR director. Single copies of *Rehabilitation Record* may be obtained for 30 cents from the Superintendent of Documents, Government Printing Office. A year's subscription is $1.75.

Plastic Technic and *Anorectal Surgery*: Dr. Guy L. Kratzer, Allentown, Pa.

A Survey of Modern Methods of Proctologic Examinations, Dr. Joseph F. Montague, New York City.

Personal Experience with 1960 Patients with Cancer of Colon and Rectum, Dr. Harry E. Bacon, Philadelphia.

The Ileostomized Patient, Dr. James P. Fleming, Rochester, N. Y.

Chemotherapy in Carcinoma of the Colon and Rectum, Drs. Richard M. Alexander and Jack W. McElwain, Great Neck, N. Y.

Closed Hemorrhoidectomy, Dr. Lynn A. Ferguson, Grand Rapids, Mich.

Management of Foreign Bodies in the Rectum, Dr. Ralph C. Venturo, Philadelphia.

Anatomical Structures Involved in Rectal Abscess and Fistulous Tract Formation (slides), Dr. Vincent A. Cianci, Providence, R. I.

Treatment of Chronic Nonspecific Ulcerative Colitis by Means of Corticosteroids Administered Rectally, Dr. John Q. McGivney, Galveston, Texas.

Radical Surgery of the Colon Cancer that Has Extended to Adjacent Organs and Tissues or Metastasized to the Liver —French Delivery, Dr. Alexander Brunschwig, New York City.

Multiple Malignancies of the Large Bowel, Dr. Joseph De Los Reyes, Los Angeles.

Information concerning this meeting may be obtained from Dr. James P. Fleming, 125 Meigs St., Rochester 7, N. Y., Secretary.

CORRECTION

Practice of Fluid Therapy.—In the Correspondence section of The Journal, Feb. 13, page 730, after the letter by Wishnofsky, there appears the following italic note. *This item was referred to the author of the original article, whose reply follows.* This statement is only partially correct. The final paragraph in Dr. Wishnofsky's letter was added after the latter had been sent to the author of the article.

An error appears in the reply to the letter. In the next to the last paragraph is a reference to Moore and others (*Ann. Surg.* 141:145 [Feb.] 1955). This reference should have been to Moore (*Ann. Surg.* 141:141 [Feb.] 1955).

EXAMINATIONS AND LICENSURE

MEDICAL SPECIALTY BOARDS

American Board of Anesthesiology: *Written.* Various locations, June 24. Final date for filing application was January 10. *Oral.* Miami Beach, April 25-30. *Applications* already on file. Sec., Dr. Forrest E. Leffingwell, 217 Farmington Ave., Hartford 5, Conn.

American Board of Dermatology: *Written.* Various locations, June 5, 1961. Final date for filing application is March 1, 1961. *Oral.* Philadelphia, Oct. 13-16. Sec., Dr. Beatrice M. Kesten, One Haven Ave., New York 32, New York.

American Board of Internal Medicine: New York City, Nov. 14-17. Closing date for filing application is July 1. *Written.* Oct. 17. Closing date for filing application is May 1. Sec.-Treas., Dr. William A. Werrell, One West Main St., Madison 3, Wis.

American Board of Neurological Surgery: Examination given twice annually, in the spring and fall. In order to be eligible a candidate must have his application filed at least six months before the examination time. Sec., Dr. Donald D. Matson, 300 Longwood Ave., Boston, Mass.

American Board of Obstetrics and Gynecology: Applications for certification in Part I, new and reopened, and requests for reexamination in Part II are now being accepted. Deadline for receipt of applications is August 1, 1960. After July 1, 1962, a minimum of three years of approved progressive residency training will be required. Training by preceptorship will no longer be acceptable. The initiation of preceptorships will not be approved after July 1, 1960. Sec., Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

American Board of Ophthalmology: *Written.* Jan. 23, 1961. Deadline for filing applications is July 1. *Oral.* San Francisco, May 9-13; Chicago, Oct. 3-7. Sec., Dr. Merrill J. King, Box 236 Cape Cottage Branch, Portland, Maine.

American Board of Orthopaedic Surgery: *Oral and Written, Part II.* Miami Beach, Jan. 3-5, 1961. Final date for filing application is July 1. Sec., Dr. Sam W. Banks, 116 South Michigan Ave., Chicago 3.

American Board of Otolaryngology: *Oral,* Chicago, Oct. 3-6. Final date for filing application was April 1. Sec., Dr. Dean M. Lierle, University Hospitals, Iowa City.

American Board of Pediatrics: *Written.* New York City, January 1961. Final date for filing application is Dec. 1. Administrative Sec., Mrs. Eleanor J. Mitchell, Rosemont, Pa.

American Board of Physical Medicine and Rehabilitation: *Oral and Written.* New York, June 17-18. Sec., Dr. Earl C. Elkins, Mayo Clinic, Rochester, Minn.

American Board of Plastic Surgery: *Oral and Written.* Milwaukee, May 1960. Final date for filing application was January 1. Corresponding Secretary, Mrs. Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8, Mo.

American Board of Proctology: *Oral and Written, Parts I and III,* Philadelphia, Sept. 24. Final date for filing application is June 30. Sec., Dr. Stuart T. Ross, 520 Franklin Ave., Garden City, N. Y.

American Board of Psychiatry and Neurology: New York, New York, Dec. 12-13. *Child Psychiatry.* Chicago, April 25-26. Sec., Dr. David A. Boyd, Jr., 102-110 Second Ave., S.W., Rochester, Minn.

American Board of Radiology: *Examination.* Cincinnati, June 6-10; Dec. 5-9. Deadline for filing applications for the June examination was Jan. 1. Filing deadline for the December examination is July 1. A special examination in Nuclear Medicine (for those diplomates in Radiology or Therapeutic Radiology) will be offered provided there are sufficient applications. Sec., Dr. H. Dabney Kerr, Kahler Hotel Bldg., Rochester, Minn.

American Board of Surgery: *Oral Examinations (Part II):* Kansas City, Kans., May 16-17, and Los Angeles, May 19-20. Sec., Dr. John B. Flick, 1617 Pennsylvania Blvd., Philadelphia 3.

Board of Thoracic Surgery: *Written.* Various centers throughout the country, Sept. 9. Final date for filing application is July 1. *Oral.* Oct. 1960. Final date for filing application is July 1. Sec., Dr. Wm. M. Tuttle, 1151 Taylor Ave., Detroit 2.

American Board of Urology: *Written.* December. *Oral-Clinical.* Chicago, February 1961. Exec. Sec., Mrs. Ruby L. Griggs, 30 Westwood Road, Minneapolis 26.

Birney, Cleanthus E., Estherville, Iowa; Kentucky School of Medicine, Louisville, 1893; fellow of the American College of Surgeons; on the staff of Holy Family Hospital, where he died Feb. 17, aged 86, of coronary thrombosis.

Bolt, William Charles, Anderson, S. C.; Medical College of South Carolina, Charleston, 1940; interned at the Grady Hospital in Atlanta, where he served a residency; fellow of the American College of Surgeons; veteran of World War II and was awarded two bronze stars for combat service; past-president of the Anderson County Medical Society; associated with the Anderson County Memorial Hospital; died Jan. 9, aged 44, of coronary thrombosis.

Brown, Charles Newton Ⓢ Marietta, Ohio; Hospital College of Medicine, Louisville, Ky., 1894; veteran of World War I; past-president of the Rotary Club of Clay County; died in the Marietta Memorial Hospital Feb. 20, aged 91.

Burns, Frederick Stanford Ⓢ Hingham, Mass.; Harvard Medical School, Boston, 1898; served on the faculty of his alma mater; formerly associated with the Massachusetts General Hospital in Boston; died Feb. 15, aged 84.

Buttz, Rose J. Piscator Ⓢ Indianapolis; Medical College of Indiana, Indianapolis, 1901; died Feb. 28.

Castle, Morrison Henry Ⓢ Cleveland; Cleveland Homeopathic Medical College, 1903; member of the Industrial Medical Association; died in the University Hospital Feb. 14, aged 81.

Colbath, William E., Adrian, Mich.; Michigan College of Medicine and Surgery, Detroit, 1893; died Feb. 8, aged 90.

Combs, Charles Nathan Ⓢ Terre Haute, Ind.; born in Mulberry, Ind., June 7, 1879; Medical College of Indiana, Indianapolis, 1903; specialist certified by the American Board of Anesthesiology; past-president and secretary of the Indiana State Medical Association; past-president, vice-president, and secretary of the Vigo County Medical Society; past-president of the Terre Haute Academy of Medicine; past-president and vice-president of the Aesculapian Society of the Wabash Valley; past-president of the Midwestern Association of Anesthetists; an honorary member of the Indiana Society of Anesthesiologists; formerly member of the House of Delegates of the American Medical Association and in 1935 secretary of the Section on Anesthesia; veteran of World War I; in 1904 joined the staff of the Union Hospital, where he subsequently served as secretary and president of the staff, superintendent, and medical director; a director of the Indiana Blue Cross Hospital Service and a member of the Indiana Advisory Hospital Planning Council; served on the editorial board of the *Journal of the Indiana State Medical Association;* wrote a "History of Medicine in Vigo County," a "History of Community Theatre in Terre Haute," a "History of the Aesculapian Society," and a "History of Union Hospital"; died Feb. 7, aged 80, of cerebral arteriosclerosis and multiple cerebral emboli.

Conyers, Chester Arthur Ⓢ Cheyenne, Wyo.; Northwestern University Medical School, Chicago, 1910; died Feb. 8, aged 78.

Cromwell, John Harold, Gooding, Idaho; St. Louis College of Physicians and Surgeons, 1903; veteran of World War I; served as county coroner, county registrar, county physician, and county health officer for many years; one of the organizers of the Gooding County Memorial Hospital; a founder of the Idaho State Tuberculosis Hospital; organizing officer and first president of the Gooding Rotary Club, in which he held an honorary life membership; a member of the Chamber of Commerce; died in Shoshone Jan. 24, aged 83.

Cronheim, Ernst Ⓢ Oakland, Calif.; Friedrich-Wilhelms Universität Medizinische Fakultät, Berlin, Prussia, Germany, 1923; member of the American Academy of General Practice; associated with the Veterans Administration Hospital; formerly practiced in Chicago, where he was on the staffs of the Louis A. Weiss Memorial Hospital and the American Hospital; died Feb. 6, aged 62.

Cunningham, Joseph Louis Ⓢ Chicago; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1907; formerly associated with the Frank Cuneo Memorial Hospital and the Columbus Hospital; died Feb. 25, aged 81.

Dietrich, Paul Henry Ⓢ Chattanooga, Tenn.; University of Pennsylvania School of Medicine, Philadelphia, 1913; fellow of the American College of Physicians; member of the Radiological Society of North America; at one time on the faculty of Loyola University School of Medicine in Chicago, and industrial surgeon for the General Motors Corporation in Pontiac, Mich.; died Feb. 28, aged 71.

Dixon, Robert Kenneth Ⓢ Detroit; University of Minnesota Medical School, Minneapolis, 1923; fellow of the American College of Physicians; served on the state board of medical examiners; for many years associated with the Mayo Clinic in Rochester, Minn.; specialist certified by the American Board of Internal Medicine; veteran of World War II; associated with Providence, Mount Carmel Mercy, and Jennings Memorial hospital; died in New Orleans Feb. 19, aged 61.

Donnelly, Frederick Clinton, Newark, N. Y.; Syracuse University College of Medicine, 1908; served as mayor and village health officer; died in the Clifton Springs (N. Y.) Sanitarium and Clinic Feb. 12, aged 76.

DEATHS

Abelmann, Theodore Carl H., Watertown, Wis.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1909; fellow of the American College of Surgeons; veteran of World War I; on the staff of St. Mary's Hospital; died in the Veterans Administration Hospital in Wood, Jan. 27, aged 73.

Adler, George Harold, Vancouver, Wash.; University of Oregon Medical School, Portland, 1927; veteran of World War I; formerly practiced in Klamath Falls, Ore., where he served as Klamath County coroner; associated with the Veterans Administration Hospital; served as a medical officer at the Veterans Administration Domiciliary at Camp White, Ore.; died in the University of Oregon Medical School Hospital in Portland, Ore., Feb. 9, aged 61.

Akana, Walter Ing Ⓜ Rome, N. Y.; Cornell University Medical College, New York City, 1926; veteran of World War II; associated with the Rose Hospital, Rome Hospital, and Murphy Memorial Hospital; died in Miami Beach, Fla., Jan. 28, aged 61, of coronary arteriosclerosis.

Anderson, James O. Ⓜ West Hartford, Conn.; Georgetown University School of Medicine, Washington, D. C., 1938; interned at the Holy Name Hospital in Teaneck, N. J.; served a residency at the Pilgrim State Hospital in Brentwood, N. Y., and the Spring Grove State Hospital in Catonsville, Md.; member of the American Psychiatric Association; veteran of World War II; formerly associated with the Norwich (Conn.) State Hospital; served as consultant at the Institute of Living in Hartford; died in St. Francis Hospital, Hartford, Feb. 14, aged 60.

Aye, Walter Albert Ⓜ Clearwater, Fla.; Western Pennsylvania Medical College, Pittsburgh, 1903; retired medical officer of the Pennsylvania Railroad; served as medical examiner for the Union Station at Chicago; died Feb. 2, aged 79.

Bach, Edwin Clarence Ⓜ Milwaukee; University of Pennsylvania School of Medicine, Philadelphia, 1922; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; served on the faculty of the Marquette University School of Medicine; associated with Milwaukee Children's and St. Mary's hospitals; a director of the Milwaukee Federal Savings and Loan Association; died Feb. 7, aged 62.

Beetem, Luther Franklin Ⓜ Madison, Ind.; University of Cincinnati College of Medicine, 1929; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; veteran of World War II; associated with King's Daughters' Hospital; died in St. Joseph's Infirmary, Louisville, Ky., Jan. 26, aged 58.

Bell, Forrest Gunn, Fresno, Calif.; Vanderbilt University School of Medicine, Nashville, Tenn., 1915; fellow of the American College of Chest Physicians; veteran of World War I; first manager of the Veterans Administration Hospital; two years ago received the national rehabilitation commission award for outstanding service to veterans from the American Legion; died in the Veterans Administration Hospital in Oakland Feb. 12, aged 67.

Bell, Peyton Elliot Ⓜ Sylvester, Ga.; University of Georgia Medical Department, Augusta, 1899; also a pharmacist; died in the Worth County Hospital Feb. 11, aged 91.

Bennett, Foster Elting, Philadelphia; Johns Hopkins University School of Medicine, Baltimore, 1948; interned at the Philadelphia General Hospital; served a residency at the Research and Educational Hospitals in Chicago, Herrick Memorial Hospital in Berkeley, Calif., and the Pittsburgh Medical Center; member of the American Psychiatric Association; from July, 1952, to July, 1954, an officer in the medical corps of the U. S. Army Reserve; certified by the National Board of Medical Examiners; served on the staff of the Philadelphia General Hospital, where he died Feb. 22, aged 35, of subacute bacterial endocarditis.

Bernard, Bethune Caldwell, Mississippi City, Miss.; University of Virginia School of Medicine, Charlottesville, 1914; veteran of World War I; died Feb. 17, aged 70.

Best, Lynwood Kent Ⓜ Charleston, S. C.; Medical College of South Carolina, Charleston, 1928; specialist certified by the American Board of Ophthalmology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; formerly resident physician at the Eye and Ear Hospital in Pittsburgh; veteran of World War II; associated with Baker Memorial Sanatorium, Roper Hospital, and St. Francis Xavier Hospital, where he died Jan. 19, aged 55, of heart disease.

Ⓜ Indicates Member of the American Medical Association.

of the Boone County Hospital and as consultant at Ellis Fischer Cancer Hospital, Columbia; died in Tampa, Fla., Feb. 12, aged 76, of coronary occlusion.

Harris, Everett Albert, Decatur, Ala.; Rush Medical College, Chicago, 1927; veteran of World War I; for many years practiced in Harvey, Ill., where he was on the staff of the Ingalls Memorial Hospital; died in the Block Chandler Hospital, Hartselle, Feb. 7, aged 65.

Harrison, Fred J., Tucson, Ariz.; Ohio Medical University, Columbus, 1898; died Jan. 12, aged 86.

Harton, Roman Albert, Durham, N. C.; Temple University School of Medicine, Philadelphia, 1934; for many years county coroner; served as jail physician and county medical examiner; died Feb. 19, aged 53.

Hyde, Williard Blackburn, Christiansburg, Ohio; Ohio Medical University, Columbus, 1904; died in the Stouder Memorial Hospital, Troy, Feb. 8, aged 78.

Jansen, Joseph Henry Jr. Ⓜ Cincinnati; University of Cincinnati College of Medicine, 1934; member of the American Academy of General Practice; veteran of World War II; died Feb. 24, aged 52.

Joseph, Benjamin Milton Ⓜ Jersey City, N. J.; University and Bellevue Hospital Medical College, New York City, 1926; member of the American Academy of Pediatrics; associated with Margaret Hague Maternity Hospital, B. S. Pollak Hospital, and the Christ Hospital, where he died Feb. 15, aged 58, of heart disease.

Karlovsky, Frank Charles, Omaha; Creighton University School of Medicine, Omaha, 1931; died in St. Joseph's Hospital Dec. 30, aged 68, of carcinoma of the lung.

Kerrick, Stanley E., Los Angeles; Minneapolis College of Physicians and Surgeons, 1908; member of the staff of the Hollywood Presbyterian Hospital, where he died Feb. 13, aged 79, of acute cardiac failure.

Kline, Arthur Charles Ⓜ Prospect, N. Y.; Albany (N. Y.) Medical College, 1904; died in St. Luke's–Memorial Hospital Center, Utica, Feb. 9, aged 80.

Langenfeld, Peter F. Ⓜ Theresa, Wis.; Northwestern University Medical School, Chicago, 1903; on the staff of St. Agnes Hospital in Fond du Lac; died Feb. 8, aged 81, of dissecting aneurysm of the abdominal aorta.

Larkin, John Francis, Kingston, N. Y.; Long Island College Hospital, Brooklyn, 1911; formerly city health officer; member of the staffs of the Benedictine Hospital and the Kingston Hospital; served on the board of managers of the Ulster County Tuberculosis Hospital; died in the Albany (N. Y.) Hospital Feb. 18, aged 74.

Laton, George Peavey Ⓜ Los Angeles; Dartmouth Medical School, Hanover, N. H., 1909; specialist certified by the American Board of Pediatrics; served on the faculty of the College of Medical Evangelists, Loma Linda and Los Angeles; veteran of World War I; for many years on the staff of the Childrens Hospital; died in the Huntington Memorial Hospital, Pasadena, Feb. 10, aged 75.

Lederfeind, Robert, New York City; University and Bellevue Hospital Medical College, New York City, 1920; member of the American Academy of General Practice; died Feb. 8, aged 66.

Lhotka, John Frank Ⓜ Butte, Mont.; Chicago College of Medicine and Surgery, 1913; a member of the staff of St. James Hospital; died Feb. 8, aged 74.

Loebel, Robert O. Ⓜ New York City; Cornell University Medical College, New York City, 1921; member of the American Society for Clinical Investigation; served on the faculty of his alma mater; died Feb. 17, aged 61.

Ludwig, Irving Ingersoll Ⓜ Chicago; Loyola University School of Medicine, Chicago, 1930; major in the medical corps, Army of the United States, from February, 1944, to July, 1948; died in Mexico City Feb. 15, aged 55.

Lynch, Mercer Genin Ⓜ New Orleans; born in New Orleans Nov. 27, 1908; Tulane University School of Medicine, New Orleans, 1932; interned at the Touro Infirmary; served a residency at the Massachusetts Eye and Ear Infirmary in Boston; assistant professor of clinical otolaryngology at his alma mater; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology, and in 1958 received its award of merit, American Laryngological Association, and American Laryngological, Rhinological and Otological Society; veteran of World War II; associated with the Eye, Ear, Nose and Throat Hospital, Touro Infirmary, and Ochsner Foundation Hospital, where he died Feb. 9, aged 51.

Maguire, Roderick Hugh Ⓜ Canton, Ill.; St. Louis University School of Medicine, 1918; died in the Graham Hospital Feb. 9, aged 69.

Mann, Salomon Ⓜ Etna, Pa.; Medizinische Fakultät der Universität, Vienna, Austria, 1915; staff physician at St. Margaret Hospital, Pittsburgh, where he died Feb. 6, aged 72.

Metzger, George Ⓜ Pittsburgh; Western Pennsylvania Medical College, Pittsburgh, 1906; died Feb. 12, aged 82.

Donovan, Daniel Raymond, Detroit; Detroit College of Medicine and Surgery, 1917; veteran of World War I and was awarded the Bronze Star; for many years examining physician for the state athletic commission; served on the staff of the Providence Hospital; died in the Veterans Administration Hospital in Dearborn, Jan. 27, aged 67, of adenocarcinoma of the sigmoid colon.

Drumm, Gerald Francis, Rochester, N. Y.; University of Buffalo School of Medicine, 1920; served as examining physician for the state department of labor; died in the Strong Memorial Hospital Feb. 18, aged 63.

Elliott, Arthur R. Ⓜ Winter Park, Fla.; born in Belleville, Ont., June 2, 1869; Queen's University Faculty of Medicine, Kingston, Ont., Canada, 1889; specialist certified by the American Board of Internal Medicine; for many years practiced in Chicago, where he was professor of medicine and president of the Chicago Post-Graduate Medical School from 1898 to 1907, professor of medicine at the University of Illinois College of Medicine from 1910 to 1915, and clinical professor of medicine at Rush Medical College from 1915 to 1927; a member of the Institute of Medicine in Chicago and its first vice-president; past-president of the Mississippi Valley Medical Society and the Chicago Society of Internal Medicine; fellow of the American College of Physicians, of which he was ex-regent and ex-vice-president; member of the Association of American Physicians; attending physician at the St. Luke's Hospital in Chicago from 1907 to 1945; in 1926 was presented an honorary LL.D. by his alma mater; died in Florida Sanitarium and Hospital in Orlando Feb. 6, aged 90, of heart failure.

Enion, George Alexander, Philadelphia; Hahnemann Medical College and Hospital of Philadelphia, 1913; veteran of World War I; served during World War II and was awarded the Legion of Merit; for many years president and later board chairman of the Industrial Life Insurance Company; on the staff of the William McKinley Memorial Hospital in Trenton, N. J.; died in the Fitkin Memorial Hospital in Neptune Feb. 10, aged 71.

Erickson, Eskil Ⓜ Halstad, Minn.; University of Minnesota Medical School, Minneapolis, 1930; interned at the Ancker Hospital in St. Paul; past-president of the Red River Valley Medical Society; member of the board of the Sunnyrest Sanatorium in Crookston, where he was on the staff of St. Francis Hospital; on the staff of the St. John's Hospital in Fargo, N. D., St. Ansgar's Hospital in Moorhead, Ada (Minn.) Municipal Hospital, and the Bethesda Hospital in Crookston; served as health officer and member of the school board; died Feb. 18, aged 58.

Evans, Hollis Clay Ⓜ New Tazewell, Tenn.; University of Louisville (Ky.) School of Medicine, 1929; associated with the Claiborne County Hospital; died in St. Mary's Memorial Hospital in Knoxville Feb. 10, aged 56.

Fleming, Major Ivy, Rocky Mount, N. C.; Jefferson Medical College of Philadelphia, 1905; for many years secretary of the North Carolina Radiological Society, of which he was president for one year; served on the staff of the Park View Hospital, where he died Jan. 26, aged 79.

Foster, Francis Vernon Ⓜ Caledonia, N. Y.; Eclectic Medical College of the City of New York, 1892; died Feb. 7, aged 90.

Friedman, Louis Ⓜ Norfolk, Va.; College of Physicians and Surgeons, Baltimore, 1912; died in the Norfolk General Hospital Feb. 16, aged 71.

Funderburk, Denver C. Ⓜ Olive Branch, Miss.; Memphis (Tenn.) Hospital Medical College, 1913; past-president of the DeSoto County Medical Society; served as mayor and city judge of Olive Branch; died Feb. 19, aged 71.

Gandy, Raymond Reeves Ⓜ Myrtle Beach, S. C.; University of Pennsylvania Department of Medicine, Philadelphia, 1899; fellow of the American College of Surgeons; for many years practiced in Stamford, Conn., where he was associated with the Stamford Hospital and St. Joseph Hospital; died Feb. 21, aged 85.

Gardenier, William Howard Ⓜ Los Angeles; Stanford University School of Medicine, San Francisco, 1935; interned at San Francisco Hospital; certified by the National Board of Medical Examiners; medical director of California Physicians Service-Bl Shield; died Feb. 22, aged 49.

George, Arthur Phillips Ⓜ Haverhill, Mass.; Dar mouth Medical School, Hanover, N. H., 1897; ve eran of World War I; for many years associate with the Hale Hospital, where he was chief of sta emeritus and past-president of staff, and where h died Feb. 17, aged 91, of cerebral hemorrhage.

Goodman, Ephraim Frank Ⓜ Bell Gardens, Calif.; University of Illinois College of Medicine, Chicago, 1933; interned at the Mount Sinai Hospital in Chicago; veteran of World War II; died in the Downey (Calif.) Community Hospital Feb. 10, aged 55.

Hall, John R. Ⓜ Colonel, U. S. Army, retired, Ashland, Mo.; Washington University School of Medicine, St. Louis, 1908; served in the regular Army from 1914 to 1948, when he retired; during World War II served as chief of hospital construction, Office of the Surgeon General, and commanded Gardiner General Hospital in Chicago; awarded the Legion of Merit; consultant, division of health of the state of Missouri; served on the medical staff

American College of Surgeons; for many years mayor of Clinton; a charter member of the Rotary Club, of which he served as president; veteran of World War I; associated with the Oklahoma General Hospital, where he died Jan. 29, aged 85.

Roth, William Fritchey Jr., Plymouth, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1931; interned at the Wyoming Valley Hospital in Wilkes-Barre; died Feb. 5, aged 53, of coronary occlusion.

Rueb, Rolland Richmond Ⓜ Mount Vernon, Wash.; Northwestern University Medical School, Chicago, 1944; interned at the Cook County Hospital in Chicago; served a residency at the Grant Hospital in Chicago; an officer in the medical corps of the U. S. Navy Reserve, from August, 1954, to August, 1956; associated with the Skagit General Hospital; died Feb. 8, aged 42.

Schuchat, William Louis Ⓜ St. Louis; Missouri Medical College, St. Louis, 1896; member of the American Academy of General Practice; associated with the Lutheran, Evangelical Deaconess, St. Anthony's, Alexian Brothers', Bethesda General, St. Mary's, and Missouri Baptist hospitals; died Feb. 4, aged 84, of a heart attack.

Schwertdtfeger, Otto Maximilian, New York City; Long Island College Hospital, Brooklyn, 1898; veteran of World War I; a member of the staff of the Lenox Hill Hospital; died Feb. 18, aged 82.

Seguin, Arthur Clement, Des Plaines, Ill.; Loyola University School of Medicine, Chicago, 1927; died in St. Francis Hospital, Evanston, Feb. 11, aged 63, of cerebral thrombosis.

Sellers, Neil Edward Ⓜ Anniston, Ala.; Medical College of Alabama, Mobile, 1905; fellow of the American College of Surgeons; associated with the Anniston Memorial Hospital, where he died Feb. 8, aged 79.

Sibley, Hartwell Astor, Boston (licensed in Massachusetts in 1904); died Feb. 13, aged 80, of heart disease.

Siders, Richard Clayton Ⓜ Redwood City, Calif.; Northwestern University Medical School, Chicago, 1943; served an internship and residency at the U. S. Marine Hospital in Chicago; his association with the U. S. Public Health Service terminated July, 1945; died Feb. 7, aged 49.

Simpson, John Wesley Ⓜ Parrish, Ala.; Memphis (Tenn.) Hospital Medical College, 1913; died Feb. 4, aged 87.

Simpson, Morrell, St. Petersburg, Fla.; Hospital College of Medicine, Louisville, Ky., 1907; on the staff of the Mound Park Hospital; formerly practiced in Bedford, Ind.; died Jan. 29, aged 77, of paralysis agitans.

Skoog, Andrew Leonard Ⓜ South Pasadena, Calif.; Northwestern University Medical School, Chicago, 1902; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychiatric Association, Association for Research in Nervous and Mental Diseases, and the Central Neuropsychiatric Association; for many years on the faculty of the University of Kansas School of Medicine in Kansas City; formerly associated with the St. Luke's, Trinity, St. Mary's, and Menorah hospitals in Kansas City, Mo.; died Feb. 5, aged 83, of injuries received when struck by an automobile.

Small, Ernest Winfield Ⓜ Belmont, Mass.; Harvard Medical School, Boston, 1902; for many years chairman of the board of health of Belmont; veteran of World War I; served as school physician; associated with Waltham (Mass.) Hospital and the Mount Auburn Hospital in Cambridge, where he died Feb. 6, aged 80.

Smyth, Francis Butler Ⓜ Bala-Cynwyd, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1936; member of the American Academy of General Practice; a staff member of the Bryn Mawr (Pa.) Hospital; died Feb. 9, aged 55, of coronary disease.

Snavely, Edmund Callaway Ⓜ Sedalia, Mo.; Barnes Medical College, St. Louis, 1905; veteran of World War I; served as county coroner and as city physician; died Jan. 27, aged 83.

Snell, Albert Markley Ⓜ Palo Alto, Calif.; born in Lake Park, Minn., June 9, 1896; University of Minnesota Medical School, Minneapolis, 1918; clinical professor of medicine, University of California School of Medicine and Stanford University School of Medicine; practiced in the Mankato (Minn.) Clinic from 1920 to 1924; came to Rochester, Minn., on Feb. 1, 1924, as a first assistant in medicine in the Mayo Clinic, where he became a member of the staff on July 1, 1925, as a consultant in medicine, and head of a section of medicine in 1929, when he became instructor in medicine in the Mayo Foundation, Graduate School, University of Minnesota, subsequently becoming assistant professor, associate professor, and professor; veteran of World War I; entered active service in the medical corps of the United States Naval Reserve on Dec. 29, 1941, with the grade of commander; commended for meritorious service by the Secretary of the Navy in 1946, and released from active duty on Feb. 16, 1946, with the grade of captain; examining member, emeritus, American Board of Internal Medicine, from 1949 to 1958; for many years a member, in 1948 vice-chairman, and in 1953 chairman of the Professional Services Division, Veterans Administration, of which he was chief of a section; in 1958 chairman of the Section on Internal Medicine, American Medical Association; past-vice-president

Meylan, George Louis Julien, New York City; New York University Medical College, New York City, 1896; retired medical director and professor of physical education at Columbia University; during World War I director of recreation for the French Army; organized various boys and girls camps in New England; died Feb. 15, aged 86.

Miller, J. Don Ⓜ Indianapolis; Indiana University School of Medicine, Indianapolis, 1908; died in St. Vincent's Hospital Feb. 10, aged 78.

Millstein, Hyman Ⓜ Southwest Harbor, Maine; Boston University School of Medicine, 1937; certified by the National Board of Medical Examiners; died Feb. 4, aged 49.

Moore, William Ⓜ Cleveland; Indiana University School of Medicine, Indianapolis, 1918; veteran of World War I; served in the regular U. S. Navy; associated with the Deaconess Hospital, where he died Feb. 19, aged 69.

Norris, Millard Fillmore Jr. Ⓜ Springfield, Ill.; Chicago Medical School, 1934; interned at St. Francis Hospital in Blue Island; veteran of World War II; died Feb. 13, aged 52.

Osterlin, Mark Frederick Ⓜ Traverse City, Mich.; University of Michigan Medical School, Ann Arbor, 1929; specialist certified by the American Board of Pediatrics; member of the American Academy of Pediatrics; past-president of the University of Michigan Pediatric and Infectious Diseases Society; served on the faculty of his alma mater; member of the board of trustees of Northwestern Michigan College; medical director of the Central Michigan Children's Clinic; associated with the James Decker Munson Hospital, where he died Jan. 29, aged 56, of a heart attack.

Oviedo, Louis Jerome Ⓜ Auburn, Calif.; University of California School of Medicine, San Francisco, 1923; served on the staff of the DeWitt State Hospital; died Feb. 9, aged 62.

Owen, Charles Keeley Kenneth Ⓜ Pittsfield, Mass.; Tufts College Medical School, Boston, 1935; interned at the Mercy Hospital in Springfield; served a residency at the New York Eye and Ear Infirmary in New York City; veteran of World War II; a staff member of Pittsfield General, Hillcrest, and St. Luke's hospitals; died Jan. 24, aged 52.

Palmer, E. Payne Ⓜ Phoenix, Ariz.; Barnes Medical College, St. Louis, 1898; past-president of the Arizona State Medical Association, Southwestern Medical Association, and the Maricopa County Medical Society; member of the American Association for the Surgery of Trauma; fellow of the American College of Surgeons, of which he was a past-governor; served on the staffs of St. Joseph's and Good Samaritan hospitals, and St. Luke's Home; died Feb. 6, aged 83.

Petty, Charles W. Ⓜ Atlanta, Ga.; College of Physicians and Surgeons, Baltimore, 1893; member of the West Virginia State Medical Association; for many years practiced in Hartford, W. Va., serving as president of the Mason County Medical Society in 1947, surgeon for the Baltimore and Ohio Railroad, and postmaster; died Feb. 5, aged 93.

Pierce, Robert S., Marianna, Fla.; Medical College of Alabama, Mobile, 1893; died in the Jackson Hospital Feb. 2, aged 90.

Pittman, Merry Elizabeth Ⓜ Quincy, Mass.; Rush Medical College, Chicago, 1938; interned at the New England Hospital for Women and Children in Boston; member of the Industrial Medical Association; industrial physician for Schrafft's Candy Factory, Charlestown; member of the staff of the New England Hospital for Women and Children, in Boston, where she died Jan. 26, aged 56.

Poser, Edward M. Ⓜ Columbus, Wis.; Rush Medical College, Chicago, 1893; served as mayor; a member of the Columbus Rotary Club; died in St. Mary's Hospital Feb. 12, aged 90.

Ransom, Loren Percy Ⓜ Syracuse, N. Y.; Syracuse University College of Medicine, 1912; served as police surgeon and team physician for Syracuse University and Nottingham High School; member of the staff of St. Joseph's Hospital; died Feb. 11, aged 74.

Resman, Louis, Buffalo, N. Y.; University of Buffalo School of Medicine, 1920; member of the American Academy of General Practice; on the staffs of the Buffalo General and Sisters hospitals; died Jan. 24, aged 65.

Robinhold, Guy Augustus Ⓜ Catawissa, Pa.; Jefferson Medical College of Philadelphia, 1919; specialist certified by the American Board of Surgery; fellow of the American College of Surgeons; past-president of the Schuylkill County Medical Society; for many years associated with the Ashland (Pa.) State Hospital and its chief surgeon until his retirement; died Jan. 31, aged 64.

Rogel, Louis Frederick, South Miami, Fla.; University of Vermont College of Medicine, Burlington, 1932; interned at Uniontown Hospital in Uniontown, Pa.; served a residency at the Veterans Administration Hospital in Roanoke, Va., and the University of Virginia Hospital in Charlottesville; veteran of World War II; on the faculty of the University of Miami School of Medicine in Coral Gables; died Jan. 29, aged 53.

Rogers, McLain Ⓜ Clinton, Okla.; Atlanta College of Physicians and Surgeons, 1902; member of the House of Delegates of the American Medical Association from 1924 to 1940; past-president of the Oklahoma State Medical Association; fellow of the

Timmerman, Ransom H., Batesburg, S. C.; Medical College of South Carolina, Charleston, 1888; served as a member of the state house of representatives; for many years a trustee of the Clemson (S. C.) College; died in the Aiken (S. C.) County Hospital Feb. 9, aged 94.

Toy, Calvert Rogers Ⓜ New Brunswick, N. J.; University of Pennsylvania School of Medicine, Philadelphia, 1923; specialist certified by the American Board of Internal Medicine; veteran of World Wars I and II; on the staffs of Middlesex General Hospital and St. Peter's Hospital, where he died Feb. 6, aged 60, of carcinoma of the liver.

Tufts, Stewart Watson Ⓜ Pittsburgh; Western Pennsylvania Medical College, Pittsburgh, 1893; died in St. Margaret's Hospital Feb. 3, aged 88.

Twiss, Henry Irving Ⓜ Framingham, Mass.; Boston University School of Medicine, 1903; veteran of World War I; associated with the Leonard Morse Hospital in Natick and the Framingham Union Hospital; died Feb. 3, aged 80, of arteriosclerotic heart disease.

Vallega, Attilio Angelo, Rutherford, N. J.; Universita degli Studi di Genova, Facolta di Medicina e Chirurgia, Italy, 1905; died in St. Mary's Hospital, Passaic, Jan. 1, aged 78.

Vinson, Noley Hugh, Falkville, Ala.; Tulane University School of Medicine, New Orleans, 1935; interned at the Employees' Hospital of the Tennessee Coal, Iron and Railroad Company in Fairfield; veteran of World War II; died in Decatur Jan. 22, aged 51.

Waldron, Martin Richard Jr. Ⓜ Seattle; Georgetown University School of Medicine, Washington, D. C., 1936; veteran of World War II; died Jan. 26, aged 50.

Walker, Alexander, Rochester, N. Y.; University of Buffalo School of Medicine, 1907; veteran of World War I; medical officer for West Irondequoit school; served on the staff of the Park Avenue Hospital, where he died Jan. 27, aged 81, of pulmonary embolism.

Walker, Irving James Ⓜ Brookline, Mass.; Harvard Medical School, Boston, 1907; specialist certified by the American Board of Surgery; clinical professor of surgery emeritus at his alma mater; member of the American Surgical Association and the International Society of Surgery–American Branch; fellow of the American College of Surgeons; formerly a member of the Board of Registration in Medicine; consultant, Malden (Mass.) Hospital and the Boston City Hospital; associated with the New England Deaconess Hospital; died Jan. 26, aged 80, of cancer of the lung.

Walker, William Getty, East Chicago, Ind.; Western Reserve University School of Medicine, Cleveland. 1956; interned at St. Luke's Hospital in Cleveland; formerly a resident at the Research and Educational Hospitals in Chicago; served on the staff of St. Catherine's Hospital; died in Indianapolis in February, aged 29.

Waluk, John, Huntington Station, N. Y.; Albany (N. Y.) Medical College, 1914; died Jan. 18, aged 76.

Warner, George Howell Ⓜ Bridgeport, Conn.; Yale University School of Medicine, New Haven, Conn., 1897; died Feb. 3, aged 90.

Watson, Seaborn Harris Ⓜ Waxahachie, Texas; Medical Department of Tulane University of Louisiana, New Orleans, 1904; died in Dallas Jan. 26, aged 81.

Webb, Charles Ferguson, Jackson, Tenn.; Vanderbilt University School of Medicine, Nashville, 1908; for many years division surgeon of the Illinois Central Railroad; a director of the National Bank of Commerce; director of the Webb–Williamson Hospital, where he died Jan. 31, aged 72, of cerebral thrombosis.

Webber, Lincoln Dean, Portsmouth, N. H.; Boston University School of Medicine, 1936; interned at the Boston City Hospital; formerly a resident at the Pondville Hospital at Norfolk, Wrentham, Mass.; served in the U. S. Naval Reserve from June, 1945, to July, 1946; associated with the Portsmouth Hospital; died Feb. 2, aged 51.

Weichselbaum, Paul King Ⓜ Chicago; University of Illinois College of Medicine, Chicago, 1938; specialist certified by the American Board of Dermatology; member of the American Academy of Dermatology and Syphilology; on the faculty of his alma mater; associated with the Research and Educational Hospital and the Grant Hospital, where he died Feb. 19, aged 46.

Weinkle, Barney, Miami Beach, Fla.; Emory University School of Medicine, Atlanta, 1917; served as city physician and coroner; associated with Jackson Memorial Hospital in Miami, and Mount Sinai and St. Francis hospitals; died Feb. 3, aged 64.

Williams, Augusta Gilbert, Norwood, Mass.; Woman's Medical College of Pennsylvania, Philadelphia, 1894; at one time practiced in Brookline, where she was a member of the school committee; formerly chief surgeon at the Vincent Memorial Hospital in Boston; during World War I was sent to France as representative of Radcliffe College with the American Red Cross; died Feb. 4, aged 94.

Wood, Jay Gould, Vining, Ga.; Atlanta Medical College, 1915; veteran of World War I; formerly associated with the Indian Service; died of heart disease Jan. 25, aged 71.

and president of the American Gastroenterological Association; past-president of the Central Society for Clinical Research; member of the American Society for Clinical Investigation, Association of American Physicians, American Association for Experimental Pathology, the Central Interurban Clinical Club, Minnesota Society of Internal Medicine, Minnesota Academy of Medicine, Society of the Sigma Xi, Alpha Omega Alpha medical honor society, Alpha Kappa Kappa, and the Alumni Association of the Mayo Foundation; fellow of the American College of Physicians; chief, division of medicine, Palo Alto Medical Clinic; member of the board of directors at the Palo Alto Medical Research Foundation; member of the board of chief consultants for the Veterans Administration; consultant in internal medicine and gastroenterology, U. S. Naval Hospital in Oakland; in October, 1951, was honored by his alma mater for his "outstanding achievements"; author of three books and author or co-author of over 200 articles in internal medicine and gastroenterology; died in the Palo Alto Hospital Feb. 6, aged 63, of coronary thrombosis.

Soe, Carl Arthur Ⓜ Shell Beach, Calif.; State University of Iowa College of Medicine, Iowa City, 1929; veteran of World War II; died in San Luis Obispo Jan. 30, aged 57.

Spannagel, William Christian, East St. Louis, Ill.; Washington University School of Medicine, St. Louis, 1903; also a pharmacist; veteran of World War I; died Jan. 17, aged 86.

Spevack, Max Ⓜ Gloucester City, N. J.; Temple University School of Medicine, Philadelphia, 1931; died in Our Lady of Lourdes Hospital in Camden Feb. 8, aged 52.

Stanley, Stephen Treat, Milford, Conn.; Columbia University College of Physicians and Surgeons, New York City, 1915; for many years a teacher in the Milford High School; died Feb. 4, aged 79.

Stetson, Thomas, Hebbronville, Texas; George Washington University School of Medicine, Washington, D. C., 1907; past-president of the Webb, Jim Hogg, Zapata Counties Medical Society; past-president of the Hebbronville Rotary Club; formerly practiced in Washington, D. C.; died in Corpus Christi Feb. 7, aged 88.

Stotler, Charles Wilbur Ⓜ Meyersdale, Pa.; Jefferson Medical College of Philadelphia, 1941; member of the American Academy of General Practice; past-president of the Somerset County Medical Society; interned at the Conemaugh Valley Memorial Hospital in Johnstown; veteran of World War II; on the staff of the Meyersdale Community Hospital; died in Pittsburgh Feb. 5, aged 43.

Suiter, David Leamon Ⓜ Oradell, N. J.; Temple University School of Medicine, Philadelphia, 1910; for many years practiced in Philadelphia, where he was associated with the Temple University Hospital; died in Paramus Feb. 9, aged 79.

Sumner, William Artell Ⓜ San Francisco; Stanford University School of Medicine, San Francisco, 1930; specialist certified by the American Board of Urology; member of the American Urological Association and in 1956 president of the Western Section; clinical professor of surgery at his alma mater; veteran of World War II; for many years chief of the Stanford urological service at San Francisco General Hospital; died Feb. 17, aged 58.

Sutton, Roscoe E., Scales Mound, Ill.; National University of Arts and Sciences Medical Department, St. Louis, 1912; died Feb. 4, aged 74.

Syvertsen, Rolf Christian Ⓜ Hanover, N. H.; Rush Medical College, Chicago, 1936; interned at Mary Hitchcock Memorial Hospital, where he was a member of the board of trustees; veteran of World War I; served as assistant to the registrar and assistant to the dean of Dartmouth College and was secretary of the medical school from 1924 to 1945, serving as assistant dean from 1944 to 1945, when was named dean; died Jan. 28, aged 63, of injuries received in an automobile accident.

Tabor, George Ewing, Houston, Texas; University of Arkansas School of Medicine, Little Rock, 1912; died Dec. 17, aged 82, of heart failure.

Tatarian, Hovsep H. Union City, N. J.; American University of Beirut School of Medicine, Syria, 1914; on the staffs of the Margaret Hague Maternity and Christ hospitals in Jersey City; for many years city physician of Union City; died Feb. 6, aged 70.

Taylor, John Proudfit, Washington, Pa.; Western Pennsylvania Medical College, Pittsburgh, 1897; died in the Washington Hospital Jan. 16, aged 88.

Taylor, Wesley Ewing, Greensboro, N. C.; University of Michigan Department of Medicine, Ann Arbor, 1899; member of the American Psychiatric Association; served on the faculty of the Atlanta School of Medicine and the Detroit College of Medicine and Surgery; served on the staffs of the L. Richardson Memorial Hospital and the Wesley Long Community Hospital; died Jan. 11, aged 85.

Terry, Willard Siddle Gilman Jr. Ⓜ Bay Pines, Fla.; Hahnemann Medical College and Hospital of Philadelphia, 1941; interned at the Hahnemann Hospital in Philadelphia and the Bayonne (N. J.) Hospital and Dispensary; served a residency at the Methodist Hospital in Indianapolis and the Receiving Hospital of the City of Detroit; associated with the Veterans Administration; died Jan. 13, aged 46, of injuries received when his automobile was struck by a train.

more such cases. In the year which ended June 30, 1959, the State Serum Institute cultured the spinal fluid of 198 patients with meningitis and by this means showed that in about 5% of all such patients Listeria monocytogenes was the cause of disease. Since the prognosis depends largely on early diagnosis and treatment with antibiotics, the possibility of this infection must be kept in mind. Three of the patients were neonates. The ages of the remaining eight ranged frcm 8 to 69 years, and the onset was characterized by progressive headache and fever for two days, often associated with gastrointestinal symptoms.

Prognosis for Aseptic Encephalitis.—In the period 1948-1958, 51 patients with "aseptic" encephalitis were treated in the Medical Department C of the Odense County and City Hospital. Possible agents were demonstrated only in three patients (poliovirus, Coxsackie virus, and adenovirus respectively). No evidence of an epidemic focus was forthcoming. Dr. P. Kildebert (*Ugesk. laeger,* Dec. 17, 1959) noted that only symptomatic treatment was given during the acute stage of the disease and that none of the patients were treated with ACTH or adrenal steroids. There were 10 deaths during the acute stage and 1 a little later. Of the 40 survivors 39 were reexamined either four or five years after they had fallen ill. In addition to 22 who could be classed as well there were 13 who showed some after-effects but whose general health and working capacity was not greatly impaired. Five had to be classed as invalids. In no case was mental retardation or secondary epilepsy recorded. Two patients, however, developed epilepsy, but they had done so long after they had recovered from their aseptic encephalitis.

Epidemic Vertigo with Hypothermia.—In 1959, Dr. A. Vaag (*Ugesk. laeger,* Feb. 11, 1960) observed five patients with acute neurolabyrinthitis which began suddenly and lasted only a day or two. The brevity of these attacks was in marked contrast to the attacks which, 15 to 20 years ago, used to last for weeks. The first patient was a 35-year-old farmer who had hitherto been well. On rising as usual at 6 a. m. he felt so giddy that he had to be supported in order not to fall. His rectal temperature was always 35.2 C (95.4 F). He suffered from nausea and nystagmus, and he needed support when he tried to sit up. Next day he had practically recovered, and his temperature was 36 C (96.8 F). Some weeks after his complete recovery his temperature ranged from 36.6 C (97.9 F) in the morning to 37.6 C (99.7 F) in the evening. The hypothermia demonstrable in some of the other patients was also associated with nystagmus and vertigo. Vaag has no facile explanation to give for the hypothermia observed in these patients, and he suggested that it might be of no great practical importance.

FRANCE

Complications Caused by Hormones.—At a meeting of the French Society of Gynecology, C. Beclerc reported the occurrence of acute abdominal complications in 25 women ranging in age from 13 to 25 years who were given excessive doses (10,000 to 13,000 units) of chorionic gonadotropin for sterility or amenorrhea. Laparatomy in all these patients revealed a large amount of blood-stained fluid in the peritoneal cavity and large tumors of the ovaries, some of which had ruptured. Microscopic examination of the specimens revealed large hemorrhagic luteal cysts.

Acenocoumarol.—Barette and Ribon (*J. méd. Lyon,* Oct. 20, 1959) gave acenocoumarol to a series of 50 patients. The anticoagulant effect was more prolonged than that of ethyl biscoumacetate. When the treatment was interrupted the prothrombinemia returned to higher than 80% within 48 hours in adults with normal liver function. Generally this drug was better tolerated by patients whose liver function was normal. On this treatment the coagulation index fell from 0.91 to 0.47 within five days. Therapeutic hypocoagulability was obtained with figures close to 0.45. The drug caused no digestive disturbance and was less toxic than other coumarin derivatives. Hematuria occurred in two patients, but it disappeared when the treatment was discontinued. The dosage varied according to the condition of the patient's liver. The usual initial dose given within 48 hours to patients with normal liver function was 56 mg. An initial dose of 46 mg. was given to patients in the older age groups, weak patients, and those with a cardiac disease or disorders in hepatic function. The maintenance dose varied between 1 and 10 mg., depending on the results of coagulation tests.

Death After Therapy with Fresh Cells.—At a meeting of the National Academy for Medicine, J. Olmer reported the occurrence of two accidents after injections of crushed fresh tissue. One patient was a 63-year-old man in whom four series of this treatment for arteritis of the lower extremities produced leukemia which led rapidly to death. Leukemia appeared three months after the last course of treatment. In the second patient three series of injections provoked progressive asthenia associated with anemia and increasing hemopathy. At first neutropenia, lymphocytosis, and the presence of erythroblastosis were noted, then myeloblasts, premyelocytes, and myeloctes appeared, and shortly before

FOREIGN LETTERS

AUSTRIA

Chamber of Physicians Objects to New Regulations.—The government of the city of Vienna issued a draft of a manual concerning the management of the Vienna city hospitals. Unfortunately the Chamber of Physicians was not asked for its opinion. Examination of the contents of this manual showed that the draft did not represent an adequate proposal for a simple and clear regulation of the agenda of hospital management. The representatives of the chief physicians and the hospital physicians had strong misgivings concerning any limitations of the duties of physicians by lay persons. The main cause was the provision in the Sick Insurance Funds Law, according to which the management of a hospital should be divided into two spheres, that of the physician and that of the nonphysician.

It should be clear that the management of a hospital must be entirely the domain of the physician. To transfer important duties in the management of a hospital to a lay person is to disregard a system that has proved eminently satisfactory for centuries. In the interest of the patients it is highly undesirable that the medical staff should be placed under the control of an administrative director who is not a physician with respect to personnel and administrative problems. The problems of nutrition of the patients, of the regulation of the service of the medical and nursing staff, and of the auxiliary personnel should be handled exclusively by the medical director.

The unjustified opinions in the draft concerning the influence of nonmedical persons on the management of a hospital have caused great unrest among the hospital physicians. The question arises why such a good and well-established system should be undermined. The hospital physicians of Vienna have made it clear that they are not ready to accept the proposed change, and they have threatened to go on strike if necessary to prevent such an action.

BRAZIL

Mansonellosis.—Mansonella ozzardi has been found in Brazil only in the equatorial state of Amazonas. It is now thought that the microfilarias of M. ozzardi, unlike Wuchereria bancrofti, do not present periodically in the bloodstream of man. Although its vector has been unknown, N. L. Cerqueira has incriminated the blackfly, Simulium amazonicum, on the basis of a recent survey. Dr. Mario P. Moraes studied a series of 33 patients infected with this filaria (*Hospital* 56:869, 1959). Blood specimens were collected from these patients at three-hour intervals between 6 a. m. and 3 a. m. the next day. In the 264 slides examined the author counted a total of 16,507 filarias with the following averages: at 6 a. m., 59.9; at 9 a. m., 74.1; at 12 noon, 73.1; at 3 p. m., 69.7; at 6 p. m., 43.8; at 9 p. m., 57.3; at 12 midnight, 58.8; and at 3 a. m., 65.9. There was no statistically significant difference between these values.

CHILE

Heredity and Hypertension.—Dr. R. Cruz-Coke (*Rev. méd. Chile* 87:699, 1959) compared the casual diastolic blood pressure levels of 120 close relatives of 35 hypertensive patients with those of 57 relatives of 17 normotensive patients. All subjects were divided into age groups, each of which comprised 10 years. The results showed a significant difference at all ages. This difference could be attributed only to the existence of hereditary factors. The 35 hypertensive patients were divided into two groups: those having primary and those having secondary hypertension. The patients with secondary hypertension had significantly higher levels than did those with primary hypertension. Comparing the diastolic pressure of the relatives of those with primary hypertension and that of the relatives of those with secondary hypertension, the author found no significant difference. This indicated that the hereditary factors come into operation with the same degree or intensity in the patients with primary and the patients with secondary hypertension. That is to say, all types of hypertensive patient had the same tensional genetic background.

The author plotted the diastolic pressure level of the hypertensive patients against that of their relatives and found a direct correlation. This showed that the diastolic blood pressure of the relatives of hypertensives increased in direct proportion to that of the hypertensive patients.

DENMARK

Listeriosis in Man.—The first case of listeriosis in man in Denmark was reported in 1958 by Jessen and Hempel-Jörgensen. Jessen and Kristensen (*Ugesk. laeger,* Feb. 4, 1960) have reported 10

The items in these letters are contributed by regular correspondents in the various foreign countries.

far were 1 to 2 Gm. daily. Such doses cause side-effects which do not occur with smaller doses. Recent comparative trials with doses of 0.25 to 1 Gm. showed the same therapeutic effect with the small dose.

A series of 19 patients, 14 of whom had retothelial sarcoma, were treated with 50-mg. tablets of prednisolone. The dosage was 400 mg. daily for five days, then 200 mg. for three days, 100 mg. and 75 mg. one day each, and then the dosage was gradually reduced in some patients to 10 mg. daily for weeks or months. Seven patients were also given treatment with x-rays or cytostatic drugs simultaneously or after two to four weeks. Fluids and salt were not generally restricted, and the patients were not given antibiotics or potassium salts. In all patients the disease was in the state of more or less advanced generalization and increasing resistance to the usual treatments at the time of treatment. Ten patients had previously been given about 30 mg. of prednisolone daily for several months. Large doses of hormone are indicated when the usual treatments fail and the disease progresses or when an acute life-threatening condition occurs. The doses of hormone were well tolerated by all patients. In a few patients autonomic disturbances occurred after three to six days, but no psychotic reactions were observed. Transient disturbance of the carbohydrate metabolism was seen in only one patient. Symptoms of pituitary basophilism were rare and not marked.

Treatment had no effect in seven patients, but nine responded dramatically. Their general condition improved within two to four days, pain disappeared, and their appetite increased. A rapid regression of the tumors was observed in a few patients. Patients with slowly progressing cases responded best. The mean duration of remission was four months. The results were no better than those achieved with other treatments, but treatment with large doses of adrenocortical hormones is indicated in patients refractory to other treatments. Patients having had this treatment frequently respond, again or for the first time, to cytostatic drugs. It should, however, be borne in mind that a stress situation may lead to adrenal failure lasting at least five days after as long as three to six months following hormone treatment and that in such a situation the hormonal deficiency must be substituted for.

Panmyelopathy.—H. H. Henneman and co-workers of Cologne (*Medizinische,* no. 29-30, p. 1340, 1959) stated that the symptoms of marrow dysplasia are anemia, leukopenia, and thrombopenia. The condition is referred to as panmyelophthisis, but this concept of the condition does not seem to apply to all cases, as the marrow findings may differ greatly while those of the peripheral blood may be similar. Although in some of the patients the marrow space is actually empty, there is another group in which cells are plentiful. The term panmyelopathy or panmyelophthisis therefore appears to apply more correctly to the second group.

A series of 50 patients with panmyelopathy was examined. All patients in whom the condition of the peripheral blood was due to systemic blood disease, splenomegaly, or hemolytic anemia had been excluded from the study. In 28 patients the marrow was found to be normoplastic or hyperplastic, and in the others it was aplastic. Anemia was the predominant condition in both groups. Only seven patients had a history of allergic disease. Nine had been taking drugs for prolonged periods, and this treatment may have been responsible for the marrow damage. The blood iron level was increased in both groups as a result of the reduced requirements, and in some patients hyperbilirubinemia was present because of acceleration in erythrocyte destruction. The spleen was sometimes enlarged, several patients had frequent intercurrent infections, and instances of hemorrhagic diathesis were observed. The erythropoiesis in the bone marrow was normal or increased. In a few patients megaloblasts and macrocytic cells were found. No alteration of the myeloid cell series, apart from a few giant stab cells, were found. Pernicious anemia, hemolytic anemia, and chronic refractory anemias with a sideroblastic marrow should be ruled out.

Examination of the same patients at various times showed that an empty marrow space may become filled and a filled space empty, that the process need not be diffuse, and that the marrow findings therefore depend on the site of puncture. Treatment is a difficult problem, and the results are often unsatisfactory. Regular blood transfusions still hold first place. Recently adrenocortical hormones have been given in large doses, but the results were not convincing. In some patients the leukopenia decreased, reticulocytes increased, and the thrombopenia was improved. Hemorrhagic diathesis was usually controllable. Panmyelopathies probably belong to the marrow dysplasias and are due to a deficiency of an unknown maturation factor.

Leukemia and Liver.—H. E. Bock and co-workers of Marburg (*Medizinische,* no. 29-30, p. 1325, 1959) stated that the liver is involved in most patients with leukemia. Differential diagnosis may be difficult in patients who have early hepatitis with severe lymphocytic or monocytic reactions. Jaundice at the beginning of leukemia may be mistaken for hepatitis. The cause of icterus occurring in the course of leukemia may be parenchymal damage, hemolytic icterus, or toxic damage due to drugs; or obstructive jaundice and leukemia may be superimposed on a serum hepatitis after frequent transfusions. Frequent blood transfusions over several years may also cause hemosiderosis. In most patients the liver death reticular cells were observed. The speaker called attention to the danger of causing tissular allergy and viral infections associated with this treatment.

GERMANY

Lupus Erythematosus.—W. Kuhn of Cologne (*Medizinische*, no. 29-30, p. 1385, 1959) stated that, although only a few years ago systemic lupus erythematosus interested only dermatologists, it has become recognized as a serious problem in internal medicine because of changes in vital internal organs associated with it. Like dermatomyositis, scleroderma, periarteritis nodosa, thrombotic thrombocytopenic purpura, and Sjögren's syndrome, it is grouped with the collagen diseases. When all the symptoms appear it is easily recognized, but in many cases there are few symptoms and the condition may be overlooked. Rheumatic fever, rheumatoid arthritis, the other collagen diseases, cirrhosis of the liver, endocarditis, malignant tumors, aplastic syndromes, and Hodgkin's disease must be ruled out in patients suspected of having lupus erythematosus.

The author described five cases. In all patients the general condition was poor. Some had fever, one had proteinuria, and one had normochromic anemia, increase of gamma globulins, and an increased sedimentation rate. Articular and renal involvement was present in four of the patients. Typical signs are the Haserick's factor, a protein in the electrophoretic range of the gamma globulins, and the L. E. cell phenomenon. Haserick's factor has an affinity for the nuclei of leukocytes and of other cells. It alters the leukocytic nucleus, which is then phagocytized by intact leukocytes. At first a number of leukocytes group around the altered nucleus in the form of a rosette. This constellation indicates, but not yet conclusively, lupus erythematosus.

When the nuclei are phagocytized, typical leukocytes are found in the blood. They possess a marginal nucleus and one or sometimes several inclusion bodies. These are usually homogeneous or of a felt-like structure. They become violet-red with Giemsa stain, and they show positive results in a Feulgen's test. Various methods have been described for demonstrating the L. E. cell phenomenon. The slide method is used routinely. Therapy with adrenocortical hormones is the treatment of choice for all patients with severe cases; 50 to 100 mg. of prednisone daily usually effects rapid decline of temperature, decline in the sedimentation rate, regression of lymphomas, and improvement in appetite. The patients feel much better. There is no connection between the severity of the disease and the number of L. E. cells per field. Chloroquine has been used in treatment.

Plasmacytoma and Macroglobulinemia.—U. Kanzow of Cologne (*Medizinische*, no. 29-30, p. 1352, 1959) stated that macroglobulinemia, which some authors consider a form of plasmacytoma, is marked by an increase of lymphoid reticulum cells in the marrow and other organs. Both diseases have a number of symptoms in common. Pain of a dragging rheumatic nature predominates in plasmacytoma, but pain is infrequent in macroglobulinemia. Deformity of bone, spontaneous fractures, and compression of vertebrae are by no means rare in plasmacytoma. Decrease of efficiency and loss in weight are early symptoms in both. Patients with macroglobulinemia have a hemorrhagic diathesis, and hemorrhages from the oral mucosa and the nose and visual disturbances occur. Patients often report that their mouths are filled with blood in the morning. The visual disorders result from retinal hemorrhages.

The anemia occurring in either disease is usually monochromic unless blood loss leads to hypochromic anemia. Leukocyte counts are uncharacteristic, and leukemia may be associated with either disease. The sternal marrow differs markedly. Reports in the literature state that the typical increase of plasma cells is found in 86% of patients with plasmacytoma. The sedimentation rate shows a maximum increase in both groups. Plasmacytoma is frequently attended by renal disturbances. Demonstrable bone defects are rare in macroglobulinemia, which in most patients occurs as a genera osteoporosis. While cell proliferations only rarel involve the spleen, lymph nodes, and liver i myeloma, enlargement of these organs is frequent in macroglobulinemia.

The cause of the hemorrhagic diathesis in this disease has not yet been discovered. A derangement of the blood protein pattern is found in either disease; alpha, beta, and gamma globulins are markedly increased in plasmacytoma. Para-amyloid deposits have been reported in various organs. The blood protein pattern typical of macroglobulinemia, which is also referred to as paraprotein, migrates in the region of the beta and gamma globulins. Ultracentrifugation studies showed that the protein body in plasmacytoma belongs to the 7 S fraction but is not identical with the normal proteins of this fraction. In macroglobulinemia the fractions 14 to 19 S predominate. These groups have group-specific and individually specific antigen determiners but not a disease-specific one, as was supposed earlier.

Prednisone for Hodgkin's Disease.—G. Stecher of Cologne (*Medizinische*, no. 29-30, p. 1379, 1959) reported that the treatment of acute leukemias and malignant diseases of the lymphatic system with large doses of prednisone has found less acceptance than might have been expected from the many favorable reports of such treatment. Doses used so are particularly prone to biliary disease. Only 22 of 340 overweight women (6.5%) had or had had a biliary disease. No instances of cholecystopathy were found in 65 obese men. On the other hand, 1,765 patients (1,265 women and 500 men) with biliary disease were grouped according to age and weight. The women in most cases weighed less than the healthy controls except for the patients 40 to 50 years old, in whom weights were average or slightly above. The average weight of the male patients, except for those 20 to 24 years old, was distinctly below normal. The authors concluded that a clear-cut correlation between body weight and cholecystopathy does not exist.

Pulmonary Hyaline Membranes of Premature Infants.—U. Keuth of Cologne (*Ztschr. Kinderh.* 82:139, 1959) stated that pulmonary hyaline membranes are caused by increased arterial CO_2 tension. Disturbances of vascular permeability cause extravasation from the pulmonary capillaries and, in a similar way, from the liver, kidneys, brain, and skin. Excess of oxygen alone is not the cause of hyaline membranes, but atelectasis and damage to the respiratory center, which causes hypoventilation, also appear to play a decisive role. Normalization of ventilation by reexpansion of atelectatic areas, resuscitation, continuous stimulation, and administration of oxygen are prerequisites for prophylaxis and treatment. Prednisone and acetazolamide have also been used.

INDIA

Trichomonal and Fungal Infections.—M. D. Narvekar and co-workers studied a series of 150 nonpregnant women who complained of leukorrhea to determine the relative incidence of trichomonal and fungal infections. The proportion was found to be about 4:7 (*J. Obst. & Gynec. India,* vol. 10, December, 1959). The incidence of fungal infections in this series was much more than that recorded in previous Indian reports. Of the 150 patients 36% had fungal infections and 21.9% had trichomonal infections. There were 130 hospital patients and 20 private patients in the series. The latter showed a higher incidence of both trichomonal and fungal infections than did the former (65% and 25% in private patients and 31.5% and 20.8% in hospital patients of fungal and trichomonal infections respectively). This difference might be due to the greater frequency of the use of systemic and local antibiotics or more frequent use of douches by private patients.

The incidence of moniliasis was greatest in patients with vulvitis and lowest in those with endocervicitis and erosion, while the incidence of trichomonads was greatest in patients with vaginitis. Of the 54 patients with fungal infection 26 had no gross local lesion although they complained of leukorrhea. Six patients showed both trichomonal and monilial infections. Thus demonstration of Trichomonas in a wet smear may not give the complete diagnosis, and culture is necessary to exclude the possibility of there being a fungal infection. Only cultural methods are reliable for diagnosing moniliasis, except in a few patients in whom the physical findings are pathognomonic. To identify the different species of isolated fungi a well-equipped laboratory is essential. Such a laboratory makes the empirical use of fungistatics in all patients with leukorrhea in whom a fungal infection has been demonstrated more rational.

Association of Physicians of India.—At the joint annual meeting of the Association of Physicians, the Association of Pediatricians, the Cardiological Society, the Neurological Society, and the Indian Association of Chest Diseases in January in New Delhi, the Prime Minister reiterated his view that it should be compulsory for all university graduates, including physicians, to work for one year or longer in the villages. He also said that students should not go abroad merely because of certain prestige attached to foreign degrees. Medical men with experience, however, should go abroad so that they can keep abreast of the rapid developments that take place in the world. He deplored the fact that by and large the medical profession catered only to those who could pay, because doing so means that a large section of the community receives no medical care. Because university education in India is a privilege, the graduates owe something to society, which granted them this privilege.

Treatment of Vaginitis.—Dhabadgao and Devi (*J. Obst. & Gynec. India,* vol. 10, December, 1959) used dequalinium chloride to treat trichomonal and monilial vaginitis and nystatin to treat monilial vaginitis due to Candida albicans. Six of their 30 patients had failed to improve with acetarsone vaginal compound. The routine treatment consisted of inserting high into the posterior fornix one vaginal suppository containing 10 mg. of dequalinium chloride at night and in the morning for eight days. This was repeated during the menstrual period for five days in gynecologic patients. No other treatment was given.

After 10 days the results were good in 25, fair in 3, and poor in 2 patients. One of the patients who showed poor results was postmenopausal and developed a severe rash all over the body after one day of treatment, which was therefore discontinued. Of the fair results, two were in patients with monilial vaginitis and one was in a patient with mixed infection; two of the patients stopped treatment after three days and the one with mixed infection was given a larger dose for three days.

is enlarged and firm. Leukemic infiltration is diffuse. It may disappear, especially with modern treatment, and periportal fibrosis may give rise to pseudocirrhosis.

The hepatic changes were investigated in a series of 236 patients with leukemia. Infiltration of the portal fields predominated in the chronic lymphadenoses, while in the myelogenous forms leukemic cells accumulated in the hepatic capillaries. Most patients had marked fatty degeneration. Their alpha-2-globulins were increased, and in the acute cases the gamma fraction was also increased. Dysproteinemia was frequent but not specific. Sulfobromophthalein retention was not related to the degree of leukemic infiltration. The serum bilirubin level was increased in 51 patients because of obstructive jaundice, marked infiltration of the liver capillaries with cells, compression of the sinusoids, or hemolytic syndromes associated with increase of indirect bilirubin and lowered osmotic resistance of the erythrocytes. In view of the fact that the drugs used to treat leukemia are cell poisons it is quite understandable that the liver cells are affected.

Triacetyloleandomycin.—W. Fuhrmann of Berlin (*Med. Klin.*, no. 42, p. 12, 1959) stated that oleandomycin phosphate was, in 1957, replaced by a new derivative, *triacetyloleandomycin* (TAO), characterized by better absorption and higher serum concentrations. Bacteria sensitive to this drug include pneumococci, streptococci, Corynebacterium diphtheriae, staphylococci, enterococci, Listeria monocytogenes, Clostridrium tetani, meningococci, gonococci, Diplococcus catarrhalis, brucellae, and Hemophilus influenzae. It is not effective against tubercle bacilli, Escherichia coli, Salmonella, Shigella, Klebsiella, Pseudomonas aeruginosa, Proteus, and yeasts. The range of action therefore corresponds to that of erythromycin.

The increase of bacterial resistance, especially of staphylococci, requires new antibiotics. Numerous tests showed that of the staphylococcic strains resistant to erythromycin, 50 to 70% still respond to TAO in therapeutic concentrations, while TAO-resistant strains were also 100% resistant to erythromycin. Extensive comparative investigations of the antibacterial activity of the two preparations showed that TAO is inferior, and this deficiency is not compensated by the higher rate of absorption. Both are mainly bacteriostatic in therapeutic concentrations. The author tried TAO for six months in the pediatric hospital. Serum concentrations were estimated in some children and found to conform to those reported for adults. The recommended dosage is 5 mg. per kilogram of body weight per day every six hours. The author also gave doses of 7.5 and 10 mg. per kilogram of body weight. The drug was readily taken by the children and well tolerated. The only side-effect was mild disturbances of intestinal motion in 4 of 48 patients which were rapidly controlled by discontinuing the treatment although it was not in all cases certain whether TAO was responsible for the disturbance.

The duration of treatment was for most patients between 5 and 10 days. Although some of the patients might have recovered spontaneously within about the same time, in most of the patients temperatures rapidly returned to normal and local symptoms disappeared when the drug was given. Some of the patients had been treated unsuccessfully with other antibiotics. The good results were most impressive in staphylococcic infections which may become the main indication for TAO. TAO-resistant staphylococci were not found with the concentration used. Some authors recommend using erythromycin first and TAO only when the organisms have become resistant. The author is not fully convinced of the rationale of this policy. In view of the danger of the development of resistance, TAO, like any other antibiotic, should be given in adequate doses.

Aerosol Treatment with Neomycin and Bacitracin.—Fricke and co-workers of Cologne (*Med. Klin.*, no. 42, p. 4, 1959) stated that the advantage of aerosol treatment is in the local effect on the epithelium and the underlying tissues. This treatment is of particular value in patients in whom the drug cannot reach the site of infection in sufficient quantity via the blood stream either because it is degraded and excreted too quickly or because insufficient blood supply, a connective tissue barrier, or a wall of infiltration prevents it from reaching the desired site. As infections accompanying bronchial carcinoma put an additional strain on the patient and increase the operative risk, the authors gave antibiotics for two to four weeks prior to operation or cytostatic treatment. Oral or parenteral treatment requires large doses of antibiotics to achieve a therapeutic concentration in the carcinomatous tissue. They therefore used a combination of neomycin and bacitracin aerosols.

The advantages of these preparations are that (1) due to their molecular weights, they are only slightly absorbed, if at all, and are effective only locally; (2) they have wide therapeutic spectrums; and (3) they do not increase resistance. The authors treated 63 patients after determining the sensitivity of the responsible micro-organisms and made the following observations: the sedimentation rate declined by 10 to 20 mm., the leukocyte count returned to normal, vital capacity increased by about 400 cc., and the amount of sputum, putrid admixtures, and dyspnea improved markedly. No intolerance to the drugs was noted.

Body Weight and Cholecystopathy.—Ries and Schröder (*Ztschr. ges. inn. Med.* 14:165, 1959) checked the widespread opinion that obese patients fibrinolysis were compared in age-matched groups of white men who had had cardiac infarction not less than three months previously, or angina pectoris in a stable phase, and white men with no evidence of cardiac disease as evidenced by history, clinical examination, sedimentation rate, and electrocardiography. The two groups were roughly matched in social and economic status and in fat and calorie consumption. Those with coronary disease who were over 50 years of age differed from the controls in having higher plasma fibrinogen levels. No significant differences were observed in blood coagulation factors.

The same factors were compared in healthy rural Bantu men and in age-matched healthy urban white men. The Bantus differed from the controls in having lower plasma prothrombin levels, better prothrombin consumption, and higher plasma levels of antihemophilic globulin. They generated more plasma thromboplastin than did the control group. Fibrinolytic activity was generally faster in the Bantu men. No differences in thromboplastin generation could be found between Bantu and white men with coronary heart disease. The significance of increased plasma fibrinogen levels in those with coronary disease was obscure. It could have been the result rather than the cause of the disease. It was suggested that during phases when fibrinolysis is inhibited, unrestricted deposition of fibrin occurs and atherogenesis is favored. In the white race, which appears to be prone to phases of prolonged lysis, severe atherosclerosis is more common than in the Bantus.

SWEDEN

Sulfamethoxypyridazine.—H. Jernelius (*Svenska läkartidningen,* Dec. 4, 1959) observed the action of sulfamethoxypyridazine in 25 patients with pneumonia and allied conditions. Since the drug is rapidly absorbed and slowly eliminated, a small dose once or twice a day suffices. On the first day 2 Gm. were given and thereafter 1 Gm. daily. Twice as much should be given to patients with severe infections such as meningitis. The concentration of the drug in the blood was measured in 11 patients and was between 5.0 and 9.5 mg. per 100 ml. 12 hours after every dose. The side-effects were insignificant and consisted of transient headache in two patients. A copious fluid intake was prescribed, and no sodium bicarbonate was needed. The treatment usually lasted 6 days (range of 3 to 14 days). The patients' ages ranged from 8 months to 78 years. Excellent results could be claimed in 64%. The drug acted in much the same way as other sulfonamides but had simplicity of administration and comparative freedom from side-effects in its favor. The results in 23 similar patients undergoing treatment with penicillin were satisfactory in 78%.

Listeriosis in Man.—Although infection with Listeria monocytogenes has been known to veterinary surgeons since 1911, no report of such an infection in man was reported in Sweden before 1958. Dr. P. Bergman and co-workers (*Svenska läkartidningen,* Jan. 1, 1960) noted that the causative organism is a gram-positive, non-spore-forming, rod-shaped facultative anaerobe. Their patient, a pregnant woman, gave birth to a dead seventh-month fetus having granulomatous changes in the skin and lungs, in which argyrophil rods were found. When the mother aborted again about six months later agglutination tests confirmed the diagnosis of listeriosis. In the same journal, Dr. S. Melander observed that, since listeriosis is so widespread in domestic animals, it may be more common among human beings than it was formerly believed to be. A search should be made for it when pregnancies come to a premature end or when they are complicated by pyelitis and fever. Dr. J. Larsson stated that since 1956, when the first case of listeriosis was reported, at least 19 others have been observed.

Sulfadon.—At the fever hospital in Lund, 70 patients were treated with the combined sulfonamide, Sulfadon. Dr. K. E. Thulin (*Svenska läkartidningen,* Jan. 15, 1960) noted that a much higher concentration was obtained in the blood than in the spinal fluid. This might explain why the three patients suffering from purulent meningitis derived so little benefit from it. The 70 patients included 17 suffering from bronchopneumonia who had reacted poorly or not at all to penicillin. They responded well to Sulfadon by a fall of temperature after 48 to 72 hours. The 18 patients who had scarlatina also responded well, and the 17 who had acute pyelonephritis or cystopyelitis showed sterile urine. The latter group required a minimum of 10 days of treatment with Sulfadon. In some patients this treatment was maintained for 21 days. The side-effects of the drug were so slight that they never necessitated its abandonment. On the whole the drug gave satisfactory results by virtue of its rapid elimination from the body and the mildness of its side-effects in spite of the large doses given.

UNITED KINGDOM

Disinfection of Blankets.—According to the *British Medical Journal* (Jan. 23) blankets are being regarded with grave suspicion in connection with hospital infection. Oiling, which prevents the dispersal of infected particles, is no longer favored mainly because of difficulties in application. Exposure to formaldehyde is of doubtful efficacy unless reinforced by heat, but even then it is not considered dependable. At the laundry, treatment with a quaternary ammonium compound has been found

After two weeks her vaginal smear showed negative results for Trichomonas but positive results for Candida, and she was then given nystatin. The subjective improvement in these patients was striking. Pruritus was relieved in most within 48 hours and vaginal discharge within five days. After two months, 12 of 15 patients with trichomonal infection had no recurrence; two of the four who had moniliasis did not report for follow-up examination and two showed no recurrence. Only one patient with trichomonal infection had a recurrence. Of those with mixed infection, five were symptom free and had smears showing negative results and one was cured of trichomonal infection but had a smear showing positive results for Candida.

Nystatin was given to eight patients with vaginitis due to C. albicans. Of this group seven had a profuse vaginal discharge, four had pruritis, and four had a burning sensation of the vulva. Two had received broad-spectrum antibiotics previously. A vaginal suppository containing 100,000 units of nystatin was inserted twice daily for eight days; this treatment was continued during menstruation. Only one patient required a second course. The response was good in five patients after eight days, and the other three were relieved somewhat. All patients were examined after one month and showed no recurrence. Vaginal discharge disappeared in about five days. Itching was relieved in 4 days in two patients and 12 days in the third. The fourth was not relieved of itching, and the vaginal swab showed positive results for Trichomonas.

NORWAY

Scandinavian Teaching Hospital in Korea.—The Scandinavian hospital, which was formally opened in Korea in December, 1958, was planned on the understanding that its staff of Scandinavian specialists in various disciplines could retire five years later and be replaced by the Koreans whom they had trained meanwhile. Dr. Atle Berg (*Tidsskr. norske laegefor.*, Feb. 1, 1960) has sought to teach his Korean colleagues how to pick and choose among outpatients those with comparatively simple cases who are suitable for admission to hospital by virtue of their value as teaching material. His Korean colleagues are learning how to discover and help the type of patient likely to respond in short time to effective treatment. Dr. L. Buer reported that 52 patients were admitted to hospital for disease of the thyroid. In view of the cost and time required for medical treatment, he has preferred preoperative iodine medication followed by subtotal thyroidectomy. Dr. R. Opsahl stated that, in addition to tuberculosis and leprosy, intestinal parasitism was common in Korea. In pleasing contrast was the comparative rarity of degenerative cardiovascular diseases. It was tempting but dangerous to jump to the conclusion that the soft and elastic quality of the aorta at the age of 70 years is attributable to the low fat content of the average Korean's diet.

Anticoagulant Therapy.—Because lifelong anticoagulant therapy of all patients with clinical atherosclerotic disease is impractical, Prof. P. A. Owren (*Farmakoterapi,* vol. 4, 1959) has tried to show where to draw the line. Prophylaxis by oral anticoagulants is effective in rheumatic heart disease when associated with one or more embolic episodes, and it should be maintained on a lifelong basis. After the first episode the patient's clinical condition, the stage of his disease, his age, and fibrillation must be taken into account, and in Owren's hospital an increasing number of such patients are given anticoagulant treatment. As the most marked reduction of mortality in both angina pectoris and myocardial infarction occurs in the first and second years of anticoagulant treatment, it has been suggested that this treatment should be discontinued after the first year or two, but this involves a risk which Owren does not feel justified in taking.

Atherosclerosis as such is not influenced by anticoagulant treatment, and the tendency to secondary thrombosis and occlusion is bound to persist. For him the duration of clinical symptoms prior to therapy is the most important factor in the selection for treatment of patients with coronary disease. Patients with angina pectoris of less than two years duration and survivors of the first attack of myocardial infarction should be given the highest priority. Patients with rheumatic heart disease who have had embolic episodes should be placed on permanent anticoagulant treatment. Patients without embolisms have to be selected on the basis of a clinical evaluation of the risk of embolism. Once a patient has been selected for treatment, after a careful consideration of all the circumstances, it should be continuous and lifelong unless contraindications should develop. Until better prophylaxis of atherosclerosis and thrombosis has been devised, prophylactic anticoagulation treatment is recommended, provided that patient and physician can intelligently cooperate.

SOUTH AFRICA

Blood Coagulation, Fibrinolysis, and Coronary Heart Disease.—A comparative blood study was made by Merskey and co-workers, of the University of Capetown (*Brit. M. J.* 1:219, 1960), of normal white men, white men with overt coronary heart disease, and normal Bantu men. The death rate from coronary heart disease is high in the white population of South Africa but extremely low in the native Bantu. Blood coagulation factors and blood

CORRESPONDENCE

COLOR DESCRIPTION

To the Editor:—In a report entitled "Argyrosis and Cyanosis—Melanosis and Cyanosis" (*A. M. A. Arch. Dermat.* 80:277 [Sept.] 1959), illustrated in color, Dr. Francesco Ronchese describes two fascinating clinical problems with special reference to the color of the skin. As usual, he documents his communication with a wide-ranging and well-chosen list of references.

One woman, in coma, was a "ghastly bluish-gray" from a combination of argyrosis and cyanosis of heart failure. A man had a color which "was really bluish-black"; his fingernails were also "bluish-black" and his urine was "coffee-black."

In the addendum Dr. Ronchese discusses color description in general. He commends my exhortation to avoid describing the nodules of lupus vulgaris as the color of apple jelly, but he misinterprets my recommendation for color description. I suggested the use of color names based on the Munsell system. I have (Appel: *Arch. Dermat. & Syph.* 62:370 [Sept.] 1950), therefore, been given a good excuse to propose once more a simple, clear, and universally recognized system of color description which is consistent with scientific nomenclature.

It is conceivable that many interested readers of our reports have never seen a cardinal's hat, a heliotrope flower, or any of the large variety of green apples. When one uses the term "salmon-red," does he mean fresh, canned, or baked salmon and does he mean the inside or the outside of the fish? What color is smoke from burning paper, from wood, and from sulfur? What color is slate? On the grounds around my house I picked up three pieces of slate of three different colors: I describe one as medium grayish-brown, one as light grayish-blue, and one as deep bluish-gray.

I suggest that colors should be described by using the names of colors. This simple proposal is based on the use of a complex system described in "The Munsell Book of Color" (Baltimore, Munsell Color Co., Inc., 1946). This complicated and expensive system is not intended to be used at the bedside or in the office. The National Bureau of Standards has already translated the technical numerical-alphabetical formula into simple words in a book called "The ISCC-NBS Method of Designating Colors and a Dictionary of Color Names" (Circular 553, National Bureau of Standards, 1955). I merely exhort my colleagues to use these names instead of such poetical and charming but highly impractical names as cardinal red, heliotrope violet, and apple green.

To describe a color, first identify the hue—red, orange, yellow, green, blue, pink, brown, etc.—and then decide on the adjective to indicate its lightness and strength. For example, to describe the color of a typical macule of pityriasis rosea, say "pale reddish-orange" or "medium orange-pink" instead of "salmon colored." To describe a pigmented mole, say "dark grayish red." The dark urine of a patient with melanosis is very dark red or blackish red.

This use of these modifying adjectives is not only clear and descriptively adequate but will also acquire quasistandard recognition (Dictionary of Color Names, p. 3):

very pale	very light	
pale	light	brilliant
light grayish	moderate	strong
	medium	
grayish		
dark grayish	dark	deep
blackish		

This method of designating colors is "sufficiently broad to be appreciated and used by science, art, and industry and sufficiently commonplace to be understood, at least in a general way, by the whole public" (Dictionary of Color Names, p. 1). The system was established to standardize descriptions by the United States Pharmacopeia and the National Formulary.

To retreat from a serious scientific work which uses words of universal clarity to describe color into the realm of flowers and stamps, however esthetically attractive, is a move backward. It is not necessary to have access to the actual color charts or even to consult these works of reference here mentioned. One needs only to stir the visual imagination ever so slightly to say "light grayish red," "moderate reddish brown," "brownish orange," or "pale purplish pink" rather than "heavenly orchid."

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TETANUS-LIKE REACTIONS

To the Editor:—The tetanus-like reactions described in The Journal by Scime and Tallant (171:1813 [Nov. 28] 1959) and Plummer and others (172:600 [Feb. 6] 1960) are usually termed dystonic or dyskinetic reactions and are well known to psychiatrists using tranquilizing drugs. These reactions usually occur within the first week of treatment and most frequently within the first three days. All effective and imparts some persistent self-sterilizing property to the blanket. Recently it has been shown that, under controlled conditions, heat can be applied without undue damage. With a nonionic detergent and sodium dihydrogen phosphate to maintain a neutral or slightly acid reaction, repeated laundering at 205 F (96 C) caused shrinkage averaging only 2.6%. A much lower temperature than this should serve to destroy vegetative bacteria, and the process might be improved. Blankets made of "terylene" or cotton, which will withstand boiling, have undergone trials, and some made of cotton have been found advantageous.

Common Colds.—C. H. Andrewes and co-workers of the Common Cold Research Unit of the Medical Research Council (*Lancet*, Jan. 23, 1960) identified and cultured viruses from patients with colds for the first time in history. The fact that these are the causative agents remains to be established. The viruses produce destructive effects in human embryonic and monkey kidney cultures. If the viruses prove to be common cold germs, the fact that they can now be grown in the laboratory opens up the possibility of producing vaccines against them.

Congenital Abnormalities.—Dr. M. J. Pleydell (*Brit. M. J.*, Jan. 30, 1960) found that in a series of 62,224 births there were 195 cases of congenital heart disease, 116 of spina bifida, 101 of harelip or cleft palate, 99 of mongolism, 64 of anencephaly, and 38 of hydrocephalus. He found evidence that anencephalic births are related to the density of the population. The incidence of anencephaly in urban districts was double that in rural districts and the incidence in the industrial belt was three times that in the rest of the county. A definite feature of anencephalic births was that they occurred in groups in time and space. It was suggested that the association between anencephaly and social class, season of the year, density of population, and grouping of births is best explained on the basis of an infectious causation. The results of a small inquiry in Northamptonshire suggested that there might be an association between Asian influenza in pregnancy and congenital abnormalities.

General Practitioner Training.—The British Postgraduate Medical Federation's experimental scheme for training general practitioners has received the unanimous approval of the General Medical Services Committee. The Nuffield Provincial Hospitals Trust is giving financial aid, and the first trainee has already completed six months of his hospital appointment. Dr. D. C. Bowie, university regional adviser on postgraduate medical education, said that the aims of the scheme were to provide training for a small number of graduates which would be adapted to their individual needs and to which general practitioners, health officers, and hospital consultants would contribute. Trainees accepted under this scheme will spend their first year in a hospital appointment, will be paid resident rates, and will be given experience in special departments according to their needs. This includes six months in the department of obstetrics and gynecology (unless such an appointment has already been held). Trainees will then go to a general practitioner for their second year, during which they will see more of the work of local health authorities and perhaps of the industrial medical services and voluntary organizations.

Penicillamine in Hepatolenticular Degeneration.—Patients with hepatollenticular degeneration have positive copper balance, and as a result copper accumulates in the brain, liver, and kidneys and is excreted excessively in the urine. Deposition of copper in these organs is associated with degenerative diseases. In the brain the basal ganglions are mainly affected, leading to the tremor-rigidity syndrome; in the liver cirrhosis occurs; and in the kidneys abnormalities of renal tubular function result in glycosuria, aminoaciduria, and phosphaturia. The basis of treatment is removal of copper by such chelating agents as dimercaprol. Walshe (*Lancet* 1:188, 1960), who found that $\beta\beta$-dimethyl cysteine (penicillamine) was the most effective decoppering agent, organized a widespread clinical trial in 16 centers involving the treatment of 22 patients.

The average age at onset was 14.8 years (range 8 to 22). The dose of penicillamine varied from 500 mg. to 3 Gm. daily, most patients receiving about 1 Gm. daily. The duration of treatment varied from four weeks to three years. Sixteen of the patients received dimercaprol alone or in combination with penicillamine. Six patients were greatly improved, 11 showed limited improvement, 3 derived no benefit, and in 2 the drug was given prophylactically. In two patients significant fading of the Kayser-Fleischer rings in Descamet's membrane was observed. One serious toxic reaction occurred in a patient who developed an arythematous rash and jacksonian convulsions. While the results showed that penicillamine was of value in the treatment of hepatolenticular degeneration, it was not known whether it removed copper or provided sulfhydryl groups for intermediary metabolism, as Walshe suggested. In most of the patients penicillamine proved better than dimercaprol in mobilizing copper and causing clinical improvement. In three patients there was either no improvement or actual deterioration despite satisfactory cupruresis. This lack of correlation between biochemical and clinical findings is one of the unsolved problems of hepatolenticular degeneration. At a cost of $20 a week it is still cheaper to treat a patient at home with penicillamine than to allow him to become bedridden and require hospital care.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

"Pure" Leprotic Neuritis. T. A. Furtado and M. S. Nankran. Arq. mineir. leprol. 19:372-379 (July) 1959 (In Portuguese) [Belo Horizonte, Brazil].

The authors report a case of leprosy in which the only clinical manifestation was the thickening of the auricular nerve, a form of "pure" isolated neuritis. The patient, a 43-year-old man, sought medical advice because of paresthetic sensations in the left cervical region, of 3 years' duration. During the last year a protrusion in the area affected was noted, together with some hyperesthesia. The auricular nerve appeared uniformly thickened, with a 3-mm. thick, 5-cm. long protrusion over the sternocleidomastoid muscle. Histological examination of a nerve fragment showed an inflammatory infiltrate containing mainly lymphocytes; there were rare granulomas, composed in the center of epithelioid cells and in the periphery of lymphocytes and a few plasma cells. Staining for leprosy bacilli showed the presence of a moderate number of isolated bacilli. The Mitsuda reaction was positive. The diagnosis of leprotic neuritis was established, and the patient was treated with a sulfone, vitamin B_1, methionine, and choline. One month later there was considerable regression of the nerve enlargement. Vitamin B_{12} was added to the therapy, and 2 months later the nerve enlargement had regressed and the paresthesia had disappeared. The authors call attention to the importance of an early detection of such leprotic manifestations.

Reversal of Antibiotic Resistance in Hospital Staphylococcal Infection. M. Barber, A. A. C. Dutton, M. A. Beard and others. Brit. M. J. 1:11-17 (Jan. 2) 1960 [London].

The incidence and drug resistance of staphylococcic infections in the surgical wards of a large general hospital have been studied over the period from Oct. 1, 1957, to June 30, 1959. In the 6 months prior to the investigation, a number of anti-cross-infection measures were introduced into the hospital, and in April, 1958, a controlled antibiotic policy was put into operation. During the investigation 5,239 patients were admitted to the wards studied, and 452 had a staphylococcic infection. The total incidence per patient of all types of staphylococcic infection fell from 10 to 7% between January and July, 1958, and thereafter remained stationary.

At the beginning of the investigation 70% of the infections were resistant to penicillin and tetracycline, and only 12% were sensitive to penicillin. At the end of the investigation 36% of the infections were resistant to penicillin and tetracycline, and 48% were sensitive to penicillin. Analysis of the strains of Staphylococcus pyogenes (on the basis of phage type) showed a similar trend toward penicillin sensitivity. Most of the infections were localized, and many were very slight, but 49 patients developed generalized infection, and 24 of these died. Forty-four of the generalized infections and 23 of the fatal infections were due to multiple-resistant strains. Twelve patients had been transferred from other hospitals for treatment of renal failure and were already infected on admission.

Multiple Myeloma: Review of 30 Cases. A. Houde, L. A. Long, R. Dussault and G. Gosselin. Union méd. Canada 89:16-32 (Jan.) 1960 (In French) [Montreal].

The authors reviewed the records of 30 patients with multiple myeloma, who were observed at the Hotel-Dieu de Montreal from 1940 to 1958. Hematological, biochemical, and roentgenologic studies were carried out on practically all the patients, but autopsy was performed on only 4 of the 24 who have died so far. Observations on these 30 patients were compared with those reported by other investigators. The male/female sex ratio was 1:1. This is unusual, since in most other reports on multiple myeloma the male patients predominated in ratios as high as 2:1. The authors note that their series is small.

During the early stage of multiple myeloma the clinical symptoms are usually extremely variable, but bone ache appears to be the most common complaint. Hematological examinations usually show normochromic and normocytic anemia, increased sedimentation rate, and *rouleau* (roller) formation of erythrocytes. Aspiration of the bone marrow permits a definite diagnosis in nearly every case. The

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The place of publication of the periodical appears in brackets preceding each abstract.

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dystonic reactions are transitory but often recur within a period of 48 hours. This fact alone can be reassuring to the patient. Although the reactions look dangerous to the unprepared observer, they usually yield readily to appropriate therapy. I am not aware of any reported deaths directly related to dystonic reactions due to tranquilizing drugs. I agree with Scime and Tallant that these reactions may be observed after receiving a small dose, but in my experience they occur less frequently than they would if a larger dose were given. The most effective treatment used by Scime and Tallant, as well as by Plummer, was intravenous injection of barbiturates. I give 0.25 to 0.5 Gm. of sodium amobarbital or 0.3 Gm. of sodium phenobarbital with prompt and satisfactory results. The effect of antiparkinsonian agents is considered to be inferior to that of barbiturates.

The confusion created by including the dystonic reaction under the parkinsonian syndrome has complicated matters. I believe that the dystonic reactions are a distinct entity separate from ordinary parkinsonism because they occur earlier in the course of drug therapy and are transitory, whereas muscular rigidity, drooling, and tremor once established are continuously in evidence as long as drug administration is continued.

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ONE POINT OF VIEW

To the Editor:—Each year since its beginning I have been a regular contributor to the American Medical Education Foundation (AMEF), believing firmly in its purposes and inspiration and grateful for the education I received, only part of which was paid for by my family at the time. In recent months I have been led to reexamine carefully my position concerning my responsibilities to the general cause of medical education.

The first consideration is that present contributions to the AMEF are grossly inadequate. The million or so dollars a year presently collected is only a pittance in confrontation with the need as stated in literature of the AMEF itself:

> In order to maintain our present physician/population ratio, the rate of medical school graduation must be 50% greater by 1975. Last year our 85 medical schools graduated approximately 7,000 physicians; in 1975 they must be expected to graduate 11,000 new doctors. These 11,000 prospective medical students will be entering high school next fall. By 1965 they will be enrolling in colleges throughout the country. In a shorter time than we care to think, they will be applying for admission to our medical schools.

Our population is climbing exponentially, literally exploding, and writers like Aldous Huxley are charging us, the nation's physicians, with "birth control" of new doctors, that is, deliberate restriction of our numbers so that we can capitalize economically on our scarcity. There is only one answer to the need, and every medical school dean knows it only too well: vast federal subsidy.

The second consideration has to do with the responsibility of providing the nation with an adequate supply of physicians. The contention that this is the responsibility of the doctors themselves is seriously open to question. Even if all of America's physicians together were able to eliminate the vast deficit of medical schools, and it is obvious that they cannot do so, would it be right or fair to make it their responsibility? Is it not the obligation of a sovereign state to see that its people have an adequate supply of physicians and medical services?

The final consideration which makes me uncomfortable about my own participation in the AMEF is the following: For over 50 years a minority of willful men in the United States Senate, together with politicians and officials in the states from which they come, have obstructed enforcement of the Constitution and Bill of Rights, have prevented representative government in the District of Columbia, and have helped to perpetuate serfdom and illiteracy in portions of the United States. The question which each conscientious physician must ask himself is whether a parallel situation exists in medical politics. Are we, who contribute to AMEF, acting as unwitting allies to a group of willful physicians who are opposed to increased federal help for anything for any purpose whatsoever and who have an unvoiced fear that federal legislation will ultimately mean forced integration of races in the nation's schools, including its medical schools? By means of the AMEF and AMA lobby in Washington, are we not doubly obstructing medical education rather than promoting it?

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COUNSEL TO AUTHORS

To the Editor:—Why do you waste 17 editorial lines telling of your Counsel to Authors announcement (*J. A. M. A.* 172:1047 [Mar. 5] 1960) without telling where it can be located, suggesting what has been changed, or saying anything in said Counsel to Authors. Your only counsel is to send for your "Suggestions for Authors . . ." reprint. Is this counsel? Either counsel or call the section "Counsel on Requesting the Reprint 'Suggestions for Authors . . .' "

J. A. T.
New York City.

Aye, aye, son. Turn to advertising section.—Ed.

Pseudoxanthoma Elasticum. G. M. Berlyne. Lancet 1:77-80 (Jan. 9) 1960 [London].

Pseudoxanthoma elasticum (Grönblad-Strandberg syndrome) is a disease characterized by widespread alteration in the elastic tissue, which produces a characteristic coarsening and elasticity of the skin, angioid streaking of the retina, and sometimes gastrointestinal bleeding which may be fatal. The cases of 2 sisters, 22 and 14 years of age, respectively, with this disease are presented. In the first patient the disease was recognized during a systematic examination for hematemesis and melena. On admission to the hospital, the patient reported that vision of her left eye had gradually deteriorated for 6 months and that 3 days before admission she had noticed that she was passing black tarry stools; before admission, the patient suffered from a fainting spell and vomited a large amount of dark red blood, containing clots. Retinal examination showed angioid streaks and perimacular pigmentation in both sisters.

Genetically, the syndrome is probably due to a recessive gene. In management of the disease, active but conservative treatment of gastrointestinal bleeding is important. The life prognosis in pseudoxanthoma elasticum is good, although patients may die of torrential gastrointestinal bleeding, or of premature coronary atheroma or hypertension. Blindness is common and is often the reason medical advice is sought. The ocular complications cannot be treated effectively.

Renal Tubular Disease with Muscle Paralysis and Hypokalemia. E. E. Owen and J. V. Verner Jr. Am. J. Med. 28:8-21 (Jan.) 1960 [New York].

The authors report on 9 female patients, between the ages of 8 and 55 years, and a 21-year-old man who were admitted to Duke Hospital in Durham, N. C., because of flaccid quadriplegia and hypopotassemia (hypokalemia). These 10 patients were found to have renal tubular disease. Nine had typical renal tubular acidosis with hyperchloremia and persistently alkaline urine. One had an as yet poorly understood renal tubular disease, characterized by excessive urinary loss of sodium, potassium, and chloride, alkalosis, hydronephrosis, nephrocalcinosis, and mental deficiency. Balance studies in several patients showed a large negative potassium balance with abnormal urinary potassium losses even during hypopotassemic attacks. Other clinical and laboratory features included polyuria, polydipsia, nephrocalcinosis, hyposthenuria, hypouricemia, and pyelonephritis, with occasional findings, during the hypopotassemic phase, of normocalcemic tetany, hyperdynamic circulation, alternating pulse, and hypophosphatemia.

Of possible causative significance was the presence or history of pyelonephritis in 8 patients. Histamine achlorhydria in one patient studied suggested a possible generalized defect in carbonic anhydrase activity. This patient's red blood cells were found to contain normal carbonic anhydrase activity, and her arterial alveolar carbon dioxide pressure gradient was normal at rest and after exercise. Although these results fail to support a generalized deficiency of this enzyme, they do not exclude a localized deficiency within the renal tubular cells.

Each patient responded well to replacement therapy with potassium and alkali, and paralysis did not recur. Renal function, as measured by blood nonprotein nitrogen value, phenolsulfonphthalein excretion, urinalysis, and intravenous pyelograms, remained normal in all patients studied, 6 of whom were under observation for 5 years or longer. Three patients no longer require potassium supplements, and one patient appears to have had a complete remission of her renal tubular disease.

Prolonged Survival of a Bone-Marrow Graft Resulting in a Blood-Group Chimera. J. O. W. Beilby, I. S. Cade, A. M. Jelliffe and others. Brit. M. J. 1:96-99 (Jan. 9) 1960 [London].

The authors report on a patient in whom a bone marrow transfusion had a successful "take," with a 9-month persistence of the donor graft resulting in the blood-group picture of a red blood cell chimera. The patient, a 30-year-old woman, was treated for several attacks of Hodgkin's disease over a period of 5 years. She received irradiation plus the administration of chlorambucil and aminochlorambucil. At the end of this period, and after the disappearance of the pruritus and night sweating which had characterized her last attack, the patient was hospitalized, complaining of lassitude, malaise, and sore throat. There was a marked fall in the hemoglobin value and number of white blood cells and platelets. Bone marrow examination showed extreme hypoplasia. The patient was given 4 pt. of blood; the hemoglobin level rose, and whereas the clinical picture continued to be serious and the platelet count continued to fall. A marrow transfusion was made, the donor being the patient's sister. The following morning there was a marked change in the clinical picture. The patient felt and looked better. She improved steadily, with a gradual rise in the white blood cell and platelet counts, and was discharged one month later, symptom free. She was still well 9 months later, with a normal blood cell count.

The patient's blood was tested with the antiserums corresponding to her own and the donor's blood genotypes 4 months after the transfusion, when all original cells from both the blood donor and the marrow donor sh [illegible] disappeared. The development of new [illegible]ns in type of myeloma can be identified by electrophoretic examination of the blood proteins. Electrophoresis of the urinary proteins seems to be superior to the chemical analysis of the Bence-Jones protein. Roentgenologic examination of the skull usually reveals typical clear, punched-out areas in patients with multiple myeloma. The prognosis is unfavorable; the disease progresses regardless of the histological type of myeloma. Therapy is of little avail, except that urethan produces a subjective, although temporary, improvement.

Recurrent Leukemia and Diseases of Reticuloendothelial System. J. Carreras Picó. Rev. clín españ. 75:107-111 (Oct. 31) 1959 (In Spanish) [Madrid].

Leukemia and malignant diseases of the reticuloendothelial system follow, as a rule, a progressively acute course to a fatal end. Remissions are rare, incomplete, and of short duration. In the course of the last few years the author observed several patients with either leukemia or malignant diseases of the reticuloendothelial system, who had recurrent, apparently complete remissions. Three cases are reported. The clinical symptoms, changes of the blood, and the myelogram prepared with material taken by sternal puncture were typical of the diseases. Sporadic remissions occurred after treatment with prednisone, blood transfusion, phenylbutazone, or antibiotics. As a rule, they coincided with the liquefaction and opening of an enlarged lymph node or of a pararectal tumor.

The remissions followed a slow course to an apparently complete recovery of the patient, with disappearance of the clinical symptoms and normalization of the blood in the hemogram; they lasted for a short period of time, and were followed by an aggravation of the diseases. Aggravation occurred unexpectedly, even in the course of treatment. It started with enlargement of the tonsils and nasal catarrh. Each new bout was more severe than the previous one, and each remission was less complete and of shorter duration. The first patient died in complete cachexia, the cause of the undulant course in him being unknown. The second and third patients are still living, in advanced stages of their diseases. The undulant course in them seemed to be an exteriorization of phases of viremia and of intracellular stages of a virus as the causal factor. One patient had undergone inoculation with a virus vaccine sometime before the appearance of leukemia.

Leukemia Following X-Ray Therapy for Ankylosing Spondylitis. D. C. Graham. A. M. A. Arch. Int. Med. 105:51-59 ((Jan.) 1960 [Chicago].

Ankylosing spondylitis was diagnosed in 591 patients at the Department of Veterans' Affairs hospitals in Toronto from 1945 to 1958. Roentgen-ray treatment was given to 146 patients, 5 of whom subsequently developed leukemia. All 5 patients died of rapidly progressive acute myeloid leukemia. No instance of leukemia was observed among the 445 patients who had not received roentgen-ray treatment. This difference in the incidence of leukemia between the radiated and nonradiated groups is statistically significant. The interval between the initial roentgen-ray treatment and the diagnosis of leukemia in these patients varied from 8 months to 8½ years, with an average of 5 years, 5 months. The interval between the last roentgen-ray treatment and the diagnosis of leukemia ranged from 1 month to 8½ years, with an average of 3 years, 9 months. A latent period as short as 8 months does not necessarily exclude an etiological relationship between leukemia and radiation exposure. It seems that there is no etiological relationship between leukemia and ankylosing spondylitis per se. It is probable that radiation injury of hematopoietic tissue is but one of several complex factors concerned in the development of leukemia in persons exposed to ionizing radiation. The potential hazard of radiation therapy for ankylosing spondylitis does not yet warrant discontinuation of this form of treatment. Hematological studies should be carried out frequently during roentgen-ray therapy. Evidence of hematopoietic injury, even the development of minor leukopenia, should probably contraindicate further radiation exposure. Repetition of courses of roentgenotherapy should be avoided unless strongly indicated.

Familial Sarcoidosis: Epidemiological Aspects with Notes on a Possible Relationship to the Chewing of Pine Pitch. R. B. Baer. A. M. A. Arch. Int. Med. 105:60-68 (Jan.) 1960 [Chicago].

Environmental influence has recently been considered as a potential etiological factor in the development of sarcoidosis. This report relates to a family of 12 siblings, 4 of whom (and possibly a 5th) have sarcoidosis. All members of the family were born and reared in a rural area, surrounded by pine trees, in southeastern Oklahoma or northeastern Texas. In childhood they had all chewed pine resin for chewing gum. This was a mixture of pine pitch and "stretchberry" (a form of huckleberry which gave a bubble-gum-like consistency to the mixture) and, in springtime, pine "buzz" (undoubtedly pine pollen, to judge from the description). On direct or written questioning of the siblings, it appeared that the 5 involved siblings chewed more of the mixture than the others. The uninvolved members claimed to have chewed mostly resin from the sweet gum (Liquidambar) tree, and almost none of the pine resin. If the theory that pine pollen is a potential etiological factor of sarcoidosis is correct, the gastrointestinal tract could be a portal of entry.

The authors feel that, if a relapse occurs after alcohol injection or electrocoagulation of the semilunar ganglion, or after decompression of the posterior root, the Spiller-Frazier technique or, better still, the Dandy method of division of the posterior root should be carried out, provided, of course, that the general condition of the patient will permit it. They advise against repeated decompressions, because sooner or later the 5th nerve will become irritated by scar formation in the retroganglionic region.

The Results of Open Commissurotomy in Acquired Calcific Aortic Stenosis: Clinical and Hemodynamic Studies in Patients Operated Upon with General Hypothermia. J. W. Gilbert Jr., A. G. Morrow and E. Braunwald. Ann. Surg. 151:1-10 (Jan.) 1960 [Philadelphia].

This report summarizes the clinical and physiological findings in 13 patients with acquired calcific aortic stenosis before and after an open operation with general hypothermia. There were 6 women and 7 men, whose ages ranged from 30 to 52 years. A history of rheumatic fever was obtained in 9 patients, and heart failure was present in 9. All the patients had normal sinus rhythm on admission, but 3 had had transient episodes of atrial fibrillation. Left ventricular enlargement was demonstrable by fluoroscopy in 11 instances, and calcification of the aortic valve in 9. The left ventricle was catheterized preoperatively in 10 patients. This procedure was valuable in the selection of patients for operation and in postoperative assessment of operative results. The indicator-dilution method has proved to be a useful technique for estimating the magnitude of aortic regurgitant flow.

Aortic valvulotomy was carried out in each patient under direct vision with the aid of general hypothermia. The period of circulatory interruption ranged from 2 to 4.5 minutes at an esophageal temperature of 29 to 30 C (84.2 to 86 F). Transient atrial fibrillation was encountered in 2 patients during operation. Ventricular fibrillation developed in 2 patients after valvulotomy and was responsible for death in one of them. Three more patients died —one of refractory ventricular fibrillation 12 hours after the operation, one of irreversible hypotension 4 hours after the operation, and one of pulmonary embolization on the 7th postoperative day. Concomitant mitral commissurotomy was carried out at the same operation as aortic valvulotomy in 4 patients and in one patient 4 months later. The 9 survivors have been followed up for 2 to 29 months (average, 17 months). All have subjectively improved, 6 of them markedly. Increased exercise tolerance has been professed unanimously, despite less convincing laboratory studies in certain instances. The experience of the authors with the open operation with hypothermia suggests that the advantages of more prolonged exposure of the valve, afforded by extracorporeal circulation, may not be fully exploited until a satisfactory prosthesis is available for valvular replacement.

Selection for Surgery of Patients with Ventricular Septal Defect and Pulmonary Hypertension. J. W. DuShane and J. W. Kirklin. Circulation 21:13-20 (Jan.) 1960 [New York].

The authors present a basic concept of operability in patients with ventricular septal defect and pulmonary hypertension. It is based not only on experience with operation in patients with ventricular septal defect but also on experience with operation in patients with pulmonary hypertension associated with patent ductus arteriosus, atrial septal defect, and other intracardiac defects. This concept of operability would become invalid should some pharmacological method become available for favorably influencing over a long period the severely elevated pulmonary resistance in patients who at present are considered to have inoperable disease.

The authors believe that the estimation of pulmonary blood flow relative to systemic blood flow, with its implications as to pulmonary and systemic resistances, becomes a critical point in the selection for operation of patients with ventricular septal defect and severe pulmonary hypertension. When pulmonary blood flow is less than systemic blood flow, the shunt being predominantly right to left, ablation of the shunt will result, not in a reduction of pulmonary flow relative to systemic flow, but in an increase. Since the greatly elevated pulmonary vascular resistance does not fall under these circumstances, pulmonary artery pressure must rise after repair, unless total cardiac output falls. Either result is probably detrimental to the patient, and operation should be avoided. When the shunt is bidirectional and of equal magnitude in the 2 directions, surgical intervention is believed to be of questionable value, since reduction in pulmonary artery pressure cannot be expected to occur. When pulmonary blood flow is greater than systemic blood flow in the presence of severe pulmonary artery hypertension, pulmonary artery pressure will be lowered by operation, and the patient will be improved or returned to normal health. In this situation operation is clearly indicated.

In occasional patients with severe pulmonary hypertension and ventricular septal defect, the decision on the advisability of operation may be extremely difficult in spite of the utilization of all techniques for assessing operability, including complete cardiac catheterization. In such borderline cases, the authors usually decide in favor of operation, with recognition of the possibility that this decision may be in error. It should be remembered that proper evaluation for operation alone cannot the patient's blood was demonstrated both qualitatively and quantitatively. There was evidence that the bone marrow graft was responsible for the production of 24% of the patient's erythrocytes. Three factors were regarded as possible cause of the development of aplasia and immune tolerance in the patient: (1) anergic effects of Hodgkin's disease; (2) irradiations; and (3) administration of large doses of aminochlorambucil. All these elements may have impaired the patient's antibody producing mechanism. The long-continued tolerance of marrow and red blood cells carrying 3 known antigens not present in the patient's own cells may be explained by 2 factors. One was the timing of the disease and of the marrow transfusion, which took place 15 days after the patient's own marrow had ceased to function; this delay may have caused the antibodies in the patient's plasma to decline, permitting the patient to become receptive to the graft. The other factor was probably the close relationship between the donor and the recipient, although the precise mechanism is not easy to discover.

Agranulocytosis Associated with Phenindione: A Case Report with Review of the Literature. A. H. Tashjian Jr. and J. P. Leddy. A. M. A. Arch. Int. Med. 105:121-125 (Jan.) 1960 [Chicago].

The authors report on a patient with granulocytopenia (agranulocytosis) associated with phenindione therapy. This was the first instance of granulocytopenia among 168 ambulatory patients given phenindione, who were followed at the Boston City Hospital. The patient was a 49-year-old woman on whom a successful embolectomy had been performed. On her discharge she was taking phenindione, 50 mg. twice daily; digitalis folia, 100 mg. daily; and penicillin G, 400,000 units daily. After 56 days of this therapy the patient was rehospitalized because of a shaking chill, productive cough, and progressive dyspnea. Serial peripheral blood and bone marrow studies were performed. The serum bilirubin level was slightly elevated. Granulocytes, more mature than myelocytes B, were at first absent in the bone marrow, but later reappeared in abundance, accompanied by a leukemoid peripheral blood response. Phenindione and penicillin G were withdrawn, but the administration of digitalis was continued throughout hospitalization. Temporary emergence of Candida albicans was observed on the second hospital day and of hemolytic Staphylococcus pyogenes var. aureus on the third. The patient recovered without the use of corticosteroids. In this case it has not been possible to demonstrate that phenindione caused the granulocytopenia, although there is no other satisfactory explanation of the disease.

SURGERY

Empirical Evaluation of Various Methods Employed in the Treatment of Trigeminal Neuralgia. H. J. Serfling and R. Unger. Beitr. klin. Chir. 199:421-429 (no. 4) 1959 (In German) [Munich, Germany].

The analysis presented in this paper is based on a total of 258 cases of true trigeminal neuralgia, which were observed over a period of 19 years at the surgical clinics of the Universities of Halle and of Greifswald. Injection of alcohol into the semilunar ganglion was employed in 174 patients during the early years. Disturbances in the sensitivity of the cornea developed in 75% of these patients; neuroparalytic keratitis, in 22 patients, of whom 3 became blind in the affected eye; and facial paralysis, in 4 patients. Relapses occurred in 25% of the patients who had been treated by alcohol injections.

Exeresis of branches of the trigeminal nerve was resorted to mostly in patients, over 70 years of age, in whom only one branch of the nerve was involved, generally the mandibular or the maxillary nerve. Three recurrences were experienced among the 21 patients in whom exeresis had been carried out from 1 to 8 years previously. In suitable cases exeresis of single branches of the trigeminal nerve can be recommended, the more so since it may prove helpful when, after electrocoagulation of the semilunar ganglion, paroxysms remain or recur in some branch of the nerve, as the authors observed in 4 cases. Electrocoagulation of the semilunar ganglion was employed in patients in whom internists advised against extensive intracranial interventions. It was carried out on 27 patients, 7 of whom had recurrences. In testing the sensitivity of the cornea, it was found to be noticeably reduced in 16 patients and slightly reduced in 4, and had remained intact in the other 7 patients.

Operations that divide the posterior root of the trigeminal nerve have proved the most effective. On the basis of their own experiences and those of others, the authors perform Dandy's operation whenever possible. On patients who cannot tolerate this major intracranial intervention, they resort to the Spiller-Frazier technique for the division of the posterior root. The following methods of decompression were used by them in 19 patients: Taarnhøjs original method of decompression (5); method of Love-Norlén (13); and Stender's method (1). It is felt that a true decompression of the posterior root is possible only by the intradural method; this procedure should be carried out only in patients who have an elastic vascular system and in whom it is desirable that the sensibility of the cornea is preserved. Extradural decompression is not reliable as regards ideal results, and the authors have been disappointed, particularly with the ophthalmological results.

right, and there were signs of pleural effusion on the left. Roentgenograms showed a homogeneous density of the entire left side of the chest. Thoracentesis produced 1,100 ml. of bloody fluid. In spite of repeated thoracenteses on 8 occasions, the patient had persistent difficulty with respiration. On exploratory thoracotomy, the lung was found to be severly compressed on its mediastinal aspect. As a cortex of 3-mm. thickness was removed, a large cystic structure was revealed, which was bounded by diaphragm, posterior mediastinum, and lung. The pathological diagnosis on the resected cystic specimen was "bronchogenic cyst."

The authors discuss the theories of the embryological development of this type of cyst, pointing out that it is closely related embryologically to bronchogenic, gastric, or enteric cysts of the mediastinum. These cysts probably form as the result of the pinching off of accessory buds from the primitive foregut or from the tracheobronchial branches, and thus might better be termed "primitive foregut cysts." Those within the esophageal wall form a distinct clinical group in that the symptomatology is quite different from that in other areas. Since these cysts may cause severe symptoms, surgical excision should be considered whenever one is discovered.

Cancer of the Lung in Women. R. E. Ottoman and J. S. Stein. California Med. 92:38-39 (Jan.) 1960 [San Francisco].

There were 35 women among the 283 patients with cancer of the lung observed at the school of medicine, University of California at Los Angeles, between April, 1955, and December, 1958. The signs and symptoms were similar to those in men, although the course seemed to be more rapid. The ages of the women ranged from 30 to 69 years, with the highest frequency in the 60-to-69 age group. The main initial symptoms were cough in 12 patients, dyspnea in 8, and fatigability in 6. The tumor was squamous-cell carcinoma in 5 patients, undifferentiated type in 11, adenocarcinoma in 9, and unclassified in the remainder. The diagnosis was established by roentgenologic examination and confirmed by cell study of the tissue obtained by thoracentesis, bronchoscopy, scalene node biopsy, or thoracotomy. Scalene node biopsy disclosed metastasis in 9 of the 11 patients on whom it was performed.

Twenty-nine patients received irradiation of the primary growth. This treatment was palliative for 11 patients and radical (tumor dose of 4,000 r or more) for 18. Only one of those receiving irradiation for palliation was alive 11 months after completion of the treatment, and only one of those receiving radical irradiation in the hope of containing the tumor survived for 20 months. In the rest of the series 2 patients with widespread lesion received only nitrogen mustard therapy, and 3 received only palliative irradiation of metastatic lesions. Five patients underwent definitive surgical treatment (pneumonectomy in 3 and lobectomy in 2) as preradiation treatment. Seven of the 29 patients treated with irradiation of the primary tumor were alive at one year after the treatment; the median survival time in this group, however, was 26 weeks.

The authors do not regard either surgery or irradiation as definitive treatment for cancer of the lung. The megavoltage therapy, though, is easy to administer and gives the patient great relief. Some results reported by an English therapy center in which only radiotherapy is used indicate the same 5-year salvage as is obtained among survivors of operation, without the mortality inherent in major surgical procedures.

Experimental Study of Polyvinyl-Formal (Ivalon) Sponge as a Substitute for Tissue. A. W. Schwartz and J. B. Erich. Plast. & Reconstruct. Surg. 25:1-14 (Jan.) 1960 [Baltimore].

The aim of the experimental studies described was to determine the effects on polyvinyl-formal (surgical Ivalon) sponge of trauma and stresses that would be similar to those imposed on Ivalon grafts in human subjects. A total of 110 implants of Ivalon sponge were made in 15 dogs. After they had been implanted with strict aseptic technique, the sponges remained imbedded for from 1 month to 7 years. The implanted sponges were subjected to various types of mechanical and thermal trauma, to radiation, to devascularization, and to local injection of strong irritants. The studies were concerned with (1) the reactions of the implant and surrounding tissues to different types of trauma; (2) the aspects of sponges remaining in animals for various periods of time with special reference to carcinogenicity, calcium deposition, and shrinkage; and (3) laboratory studies on Ivalon sponges, including tinctorial characteristics and response to the digestive action of bacterial cultures.

Although satisfactory in many ways, one of the main objections to Ivalon sponge as a replacement for soft tissue is its tendency to become firm and to undergo shrinkage. Living tissues, though, seem to tolerate Ivalon well. No appreciable deterioration and no signs of foreign-body irritation are observed in Ivalon implants if strict sterile technique is followed. The formation of fibrous tissue was most pronounced in the group of sponges submitted to strong irritation, such as mechanical trauma, injections of sodium morrhuate, and thermal and x-ray burns. The formation was less in the group in which irritation was of medium or mild degree (alternation of blood supply and free full-thickness skin grafting), and little fibrous tissue developed in the group in which irritation was not produced. The deposition of calcium seemed to be related assure uniformly good results, since the method of conduct of the operation, the perfusion, and the postoperative care determine the results.

Successful Resection of Ventricular Aneurysm: Case Report. J. J. Sullivan Jr., J. L. Mangiardi and D. E. Janelli. Ann. Surg. 151:22-25 (Jan.) 1960 [Philadelphia].

A 44-year-old man was hospitalized in 1956 for evaluation of a suspected pheochromocytoma. He had had several episodes of precordial tightness associated with severe hypertension since 1949. The attacks had promptly subsided with rest and sedation. A postinfarctional left ventricular aneurysm was revealed by roentgenogram of the chest on admission. A retroperitoneal exploratory operation for a suspected left adrenal medullary tumor showed no evidence of tumor. One week later, lateral thoracotomy on the left was performed by way of the 5th interspace, exposing a ventricular aneurysm. Resection of the aneurysm was carried out successfully by closed methods, although embolization developed, resulting in motor aphasia and right hemiplegia. These disorders have cleared completely, and the patient is well and working 3 years later.

The etiology of the paroxysmal hypertension in this patient is not clear. His hypertension remained unaltered by operation. The myocardial infarction probably occurred in 1952 but was unrecognized at that time. The aneurysm developed during the 4 years preceding the operation. Utilization of closed methods for the surgical treatment of ventricular aneurysm is feasible in some instances, but it carries a risk of embolization. Open cardiotomy, with cardiopulmonary bypass by means of a pump-oxygenator, seems to be the preferred method.

Leiomyomas of the Esophagus. L. Büchter and J. Huth. Beitr. klin. Chir. 199:385-395 (no. 4) 1959 (In German) [Munich, Germany].

The authors list the various benign tumors of the esophagus, giving particular attention to reports on surgically treated leiomyomas. The male/female sex ratio of esophageal leiomyomas is 2:1. The patients are mostly young or middle-aged, at any rate younger than the patients with carcinoma. The leiomyomas originate in the longitudinal and circular musculature of the esophageal wall or in the muscularis mucosae. They are most frequent in the lower third of the esophagus. They are of solid consistency, and either grow in the form of nodular-lobular formations within the esophageal musculature, or surround the esophagus as circular or horseshoe-shaped growths. Histological examination reveals a fascicular structure. Some leiomyomas are interspersed with collagenous connective tissue fibers, and are referred to as leiomyofibromas. In large tumors, circulatory disturbances may lead to edema, hemorrhage, fatty degeneration, or necrosis, with deposition of calcium salts. The clinical diagnosis of esophageal leiomyomas is difficult, because symptoms are few or nonexistent and the patients are relatively young. The various roentgenologic methods used in the diagnosis are evaluated. Early surgical treatment is advisable to make certain that the growth is not a malignant one, to forestall progressive growth of the leiomyoma which will make operation too difficult, to prevent malignant degeneration, and to overcome dysphagia.

The authors present the histories of 3 patients operated on for leiomyomas of the esophagus at the surgical clinic of the University of Halle. One was a 45-year-old man, and the other 2 were women, aged 29 and 43 years, respectively. The growths of all 3 were removed, one by resection of the cardia and by esophagogastrostomy, another by enucleation and resection, and the third by enucleation. All 3 patients recovered, and have remained free from symptoms.

Esophageal Cysts. G. Desforges and J. W. Strieder
New England J. Med. 262:60-64 (Jan. 14) 196
[Boston].

Esophageal cysts may be asymptomatic, or the
may cause several different syndromes. Of the
patients whose histories are presented, one had a
asymptomatic form; the second had a syndrome
dysphagia secondary to luminal compression; an
the third had hemothorax secondary to the esoph
geal cyst. The first of the 3 patients was a 24-yea
old man who had a cough, aggravated by hea
smoking. When chest films revealed a parahil
density, a thoracotomy was performed, and a c
was found presenting from the esophagus; it w
shelled out, and the patient recovered. The pa
hilar density noted on roentgenologic examinat
was caused by the enlarged hilar lymph nodes;
cyst was not evident in the film. The patholog
diagnosis was "branchial-cleft cyst."

The second patient, a 32-year-old man, presen
himself at the hospital with the complaint of co
plete obstruction to swallowing of 4 days' durat
He dated his symptoms to the ingestion of a la
bolus of turkey meat. In addition to the diffic
in swallowing, there had been marked locali
discomfort at the level of the midsternum each t
he attempted to swallow. At operation, a mov
mass was found beneath the esophageal musc
coat immediately below the carina. The overl
muscle was split, and the mass enucleated.
valescence was uneventful. The pathological re
was "benign embryonic structure, apparentl
respiratory-tract origin."

The third patient, a 20-year-old woman,
plained that 4 days before admission, while at
she was suddenly seized with substernal pain.
was severly dyspneic, the trachea was shifted t

Successful management of congenital megacolon begins with recalling the defect whenever symptoms and signs of acute intestinal obstruction occur in an infant. After a thorough history and physical examination, plain and barium-enema roentgenograms of the abdomen should be taken. If aganglionic megacolon is then suspected, the distended abdomen can often be relieved by insertion of a small rectal tube and gentle irrigation of the colon with warm saline solution. The physician should perform these irrigations rather than relegate them to a nurse. In children who are dehydrated owing to gastroenteritis, fluids should be infused, and then further diagnostic procedures can be carried out. Unnecessary explorations of infants with megacolon, with a mistaken diagnosis of obstruction of the small intestine, can be avoided by a barium-enema examination, but rectal biopsy offers the only way of making an accurate diagnosis of megacolon in the neonate. The authors recommend a colostomy as soon as the diagnosis is established. They delay resection of the aganglionic segment until the child attains a weight of 9.1 to 13.6 kg. (20 to 30 lb.).

Complete Repair of a Syndrome of Congenital Defects Involving the Abdominal Wall, Sternum, Diaphragm, Pericardium, and Heart; Excision of Left Ventricular Diverticulum. D. G. Mulder, I. H. Crittenden and F. H. Adams. Ann. Surg. 151:113-122 (Jan.) 1960 [Philadelphia].

The authors report on 3 patients with a new syndrome having the following characteristics: malrotation of the heart with dextroposition, intracardiac anomalies including ventricular septal defect, defective lower sternum, anterior diaphragmatic hernia, pericardial defect and deficient abdominal wall with diastasis recti, and umbilical hernia. One patient, at the age of 15 months, was explored through a median sternotomy and upper midline abdominal incision. The zyphoid and lower portion of the sternum were absent. The deficiency of the midline structures included a 3-cm. anterior diaphragmatic defect as well as diastasis recti and umbilical hernia. A 3.5-cm.-long diverticulum enclosed in a tubular pericardial sac arose from the apex of the left ventricle and projected through the diaphragmatic defect and diastasis recti into the epigastrium. It was pulsatile and filled synchronously with each cardiac cycle. The heart was dextroposed, and there was a thrill over the right ventricular outflow tract.

The patient was placed on extracorporeal circulation, and the heart arrested with Melrose potassium citrate solution. The left ventricular diverticulum was clamped at its base and amputated. The stump was closed with a double-run continuous no. 4-0 silk suture. A right ventriculotomy was then made, and a 1.5-cm.-high membranous ventricular septal defect was closed with interrupted sutures of fine silk. The heart beat returned promptly on the release of the aortic cross-clamp, and no cardiac arrhythmias developed. The pericardial and diaphragmatic defects were readily closed by interrupted sutures of fine silk. The diastasis recti and the umbilical hernia were similarly repaired. The edges of the cleft sternum were approximated with interrupted wire sutures. The patient tolerated the operation well, and his postoperative course was uneventful. It was possible to repair all anomalies in this patient in one operation, because he had correctable cardiac pathology and relatively less severe deficiencies of the other component anomalies. Since submitting the manuscript, the other 2 patients in this series have been operated on successfully.

NEUROLOGY & PSYCHIATRY

Epidemic Vertigo: Clinical Picture, Epidemiology, and Relation to Encephalitis. E. Pedersen. Brain 82:566-580 (no. 4) 1959 [London].

The author analyzes the clinical symptoms and the epidemiologic background in 144 patients with epidemic vertigo, who were observed in the course of several epidemics in Denmark during the past 10 years. The histories of 16 hospitalized patients are given. The disease occurred in both urban and rural districts, and no predilection for any particular season of the year was noticed. No evidence which might suggest a relationship between the disease and areas of water or milk supply could be found. The patients had not been in contact with domestic animals. Observations suggest that the disease may be spread by carriers.

The epidemiologic investigations suggest that epidemic vertigo and encephalitis may have the same etiology, since both occurred in the same outbreak. The clinical pictures observed during these epidemics were mixed, but 2 types of disturbances were predominant. In some patients the initial symptoms were a gastrointestinal reaction and fever, with an incubation period of 1 or 2 days, and in others an upper respiratory infection, with an incubation period of 12 to 14 days. During the course of the disease, the character of the vertigo often changed. At first it occurred in episodes of long duration or was constantly present, while later on it became paroxysmal, at this stage being frequently provoked by rapid movements of the head or trunk. The course of the disease was short and benign in most cases, but 5 to 10% of the patients had symptoms, in particular, extreme fatigue, depression, and paroxysmal vertigo, which persisted for prolonged periods and which were often incapacitating. The cause of epidemic vertigo should more to the time element than to the presence of irritants. Sponges which had remained in animals for years showed more calcium deposition than did those implanted for shorter periods. None of the sponges induced neoplastic changes, not even those that were imbedded for 7 years.

In laboratory studies it was shown that Ivalon is not digested or otherwise visibly affected by the digestive action of various bacteria. It appears that in many instances Ivalon sponge is a suitable substitute for living tissue, but further changes (possibly in the manufacturing process) will be necessary before a polyvinyl material can be produced that is, in every respect, an ideal substitute for living tissue.

Thyroid Carcinoma: Diagnosis and Management. G. H. Martin. J. Mississippi M. A. 1:7-10 (Jan.) 1960 [Fulton, Mo.].

Carcinoma of the thyroid remains a controversial subject, although certain areas of agreement have been reached. Malignant tumors of the thyroid occur most frequently in solitary, nontoxic nodules in young women. It is often impossible to make a definitive diagnosis of carcinoma of the thyroid on frozen sections. Solitary nodules of papillary carcinoma should be treated by total thyroidectomy. In the absence of clinical evidence of lymph node metastasis in papillary carcinoma, prophylactic neck dissection is not indicated. Papillary carcinoma with lymph node metastasis should be treated by total thyroidectomy and modified unilateral neck dissection. Undifferentiated intracapsular thyroid carcinoma should be treated by total thyroidectomy plus unilateral radical neck dissection. Undifferentiated carcinoma with extracapsular infiltration is probably best treated by biopsy alone, followed by palliative postoperative management. Roentgen-ray therapy is of palliative value, especially in bone metastasis. Radioiodine (I^{131}) has proved to be of little value. Suppression of the pituitary thyroid-stimulating hormone is indicated in all patients with a history of thyroid cancer. The prognosis in thyroid carcinoma varies with the type of malignancy, being good in papillary adenocarcinoma, poor in small-cell carcinoma, and nil in giant-cell carcinoma.

Acute Appendicitis Associated with Meckel's Diverticulum. E. B. Smith. J. Nat. M. A. 52:51 and 73 (Jan.) 1960 [New York].

During a 15-month period while on duty at the U. S. A. F. Hospital, Elmendorf Air Force Base, Alaska, the author observed 6 cases of Meckel's diverticulum associated with acute appendicitis. The indication for surgical exploration in all these cases was the clinical picture of acute appendicitis. Three illustrative case histories are presented. The ages of the 3 male patients ranged from 19 to 22 years. In the first patient exploration through a modified McBurney's incision revealed a suppurative retrocecal appendix and an injected Meckel's diverticulum. The appendix was removed and the diverticulum resected, with end-to-end anastomosis. In the second patient a greatly inflamed and edematous retrocecal appendix was found. A Meckel's diverticulum was noted approximately 2 ft. from the ileocecal valve. In addition to an appendectomy, a diverticulectomy was performed. The third patient had a suppurative appendix and a Meckel's diverticulum, approximately 2 ft. proximal to the ileocecal valve. An appendectomy and a diverticulectomy were performed.

The author stresses that the terminal ileum, for at least 3 ft., should be explored during appendectomy, regardless of the pathological state of the appendix. Meckel's diverticula occur in approximately 2% of all persons. The possible complications of hemorrhage, ulceration, inflammation, obstruction, and intussusception make removal of a Meckel's diverticulum a necessary procedure when discovered during an appendectomy.

Similarities of Mechanical Intestinal Obstruction and Aganglionic Megacolon in the Newborn Infant: A Review of 64 Cases. O. Swanson and F. Z. Davidson. New England J. Med. 262:64-67 (Jan. 14) 1960 [Boston].

The authors point out that neonates with aganglionic megacolon (Hirschsprung's disease or neurogenic obstruction) frequently have the signs and symptoms of acute intestinal (mechanical) obstruction. Because of this similarity between neurogenic and mechanical obstruction of the lower intestine, clinical impressions are often misleading. Of 64 infants under one year of age, who presented with congenital aganglionic megacolon between 1950 and 1958, 47 had the classic signs and symptoms of acute intestinal obstruction, such as abdominal distention, constipation, and vomiting. During the same period 9 infants with ileal obstruction were operated on; 8 of these had vomiting, constipation, and abdominal distention, and the 9th had abdominal distention.

In the 64 infants with congenital megacolon in whom a surgical procedure was used to relieve the obstruction, 27 colostomies and 37 primary resections with pull-through anastomosis were performed. There were 5 deaths after colostomy and 4 deaths after primary resection. Nine postoperative deaths among 64 patients (14%) were deemed excessive, although much higher death rates had been reported as late as 1954. Over a period of years, the authors have changed their policy with regard to the treatment of children with congenital megacolon. While their evidence is not yet conclusive, they consider it unwise to perform a one-stage resection on neonates.

brain tissue. The superficial portions of the cerebral tract were sucked away, and the tract was irrigated. The patient continued to exhibit signs of progressive mental deterioration, elevated temperature, and bilateral tremor and rigidity for several weeks before death.

The pathological examination was limited to the brain. It revealed the bilateral chemical destruction of the ventromedial portion of the globus pallidus, which, however, had no lasting effect on the rigidity or tremor of parkinsonism. Demonstrated once again is the lack of a precise understanding of the neurophysiological significance of pallidal function in paralysis agitans. That the intracerebral injection of Etopalin carries risk is proved by the ability of this liquid to separate and advance along fiber tracts for a considerable distance. In this case the solution of alcohol and ethyl cellulose was injected with sufficient pressure to permit passage across the anterior commissure to the medial part of the globus pallidus opposite. The injury resulting from the injection of alcohol was characterized by coagulation necrosis and marked hemosiderosis.

Proximal Occlusion of the Anterior Cerebral Artery.

J. E. Webster, E. S. Gurdjian, D. W. Lindner and W. G. Hardy. A. M. A. Arch. Neurol. 2:19-26 (Jan.) 1960 [Chicago].

Between September, 1948, and January, 1958, the authors detected by angiographic studies 50 patients with nonfilling or thread-like filling of the proximal portion of one anterior cerebral artery associated with neurological and/or psychiatric (dementia, impaired insight, anxiety, loss of initiative, and impaired mentation) signs and symptoms. Data on these 50 patients are tabulated and discussed. Nonfilling or thread-like filling in angiographic studies of the proximal portion of the anterior cerebral artery may be due to occlusive atherosclerosis or to congenital abnormalities, with a small proximal anterior cerebral artery on one side or the other. Although the incidence of a small proximal anterior cerebral artery on one side in routine autopsies is about 2%, among patients with cerebrovascular disease, with symptoms and signs, small or nonfilling proximal anterior cerebral arteries were found in 11% in the series studied by the authors.

Aging of the vessels in conjunction with congenital maldevelopment may, therefore, result in dysfunction of the proximal portion of the anterior cerebral artery, particularly involving the ganglionic branches (including the artery of Heubner) to the hypothalamus, corpus striatum, and anterior portion of the internal capsule. This type of disturbed cerebral circulation may result in both neurological and psychiatric disturbances, which include vague psychiatric features with weakness, anxiety, and poor mentation, probably related to hypothalamic derangement. Weakness of the contralateral half of the body, greatest in the upper extremity, is also present in more than one-third of the patients.

The diagnosis of occlusion of the proximal anterior cerebral artery may be made by angiographic studies. As an aid in diagnosis, contralateral digital carotid artery compression may be used. This will frequently result in syncope associated with grasping upper-extremity movements. A positive carotid artery compression test with syncope, resulting from compression of one or the other carotid artery in the neck, may serve to distinguish organic from functional disease, particularly in patients over 40 years of age. Angiographic studies in such cases may define the diagnosis more accurately.

Study of Mesencephalic Tegmentum in Paralysis Agitans and Parkinsonism.

E. A. Spiegel, H. T. Wycis, E. G. Szekely and others. A. M. A. Arch. Neurol. 2:46-55 (Jan.) 1960 [Chicago].

This study deals with the electrogram of the midbrain tegmentum in man and the influence of this region upon the electromyogram and the electroencephalogram, chiefly in patients with parkinsonian symptoms. It is part of a project attempting to influence static tremor, rigidity, and spasticity by placing lesions in an area remote from the pyramidal tract. The authors restricted the region where stimulating and lesion-producing electrodes were inserted to the oral mesencephalon with the posterior commissure as a reference point. A triple electrode was inserted in an area ventral to the periaqueductal gray matter, dorsal to the nucleus ruber, lateral to the oculomotor roots, and medial to the spinothalamic tract. The present series includes 20 patients: 9 with idiopathic paralysis agitans; 8 with postencephalitic and 1 with posttraumatic parkinsonism; and 2 with cerebral palsy accompanied by marked spastic paralysis and athetoid movements.

It is concluded that the tremorigenic area in parkinsonism is located chiefly caudal to the oral mesencephalic tegmentum. The hypothesis is submitted that the extent and localization are subject to fluctuations. On stimulation of this area with rhythmic pulses or with direct current, a latent tremor might become manifest, or the amplitude and/or frequency of an existing tremor might be increased. After inducing circumscribed lesions of the area (mesencephalic tegmentotomy), a reduction of the tremor, chiefly in the opposite extremities, was observed initially in 77% of the cases; however, this result was maintained in only 55%. The electroencephalogram revealed in 9 of 14 cases the appearance of theta waves or an accentuation of preoperatively existing theta waves; in 2 of these 9 cases high-amplitude delta waves also appeared, chiefly in the frontal, temporal, and central leads. These changes were transitory.

be sought in the brain stem, but as the disease is infectious in nature, it is possible that the localization varies from patient to patient in both the central and the peripheral vestibular system.

Anteriographic Study of Cerebrovascular Disease in Man: I. Stenosis and Occlusion of the Vertebral-Basilar Arterial System. J. S. Meyer, S. Sheehan and R. B. Bauer. A. M. A. Arch. Neurol. 2:27-45 (Jan.) 1960 [Chicago].

The authors have been examining patients with cerebrovascular accidents, admitted to the Detroit Receiving Hospital, by bilateral angiography of the common carotid artery and retrograde arteriography of the subclavian-vertebral arteries, in order to determine the pattern and frequency of involvement of the cerebral vessels by atherosclerosis, since this information is of importance in deciding the relative merits of medical and surgical treatment. The use of angiography in cases of cerebrovascular disease requires caution, since experience with iodopyracet (Diodrast) indicated that this radiopaque substance is damaging to vascular endothelium and may increase the incidence of thrombosis. The authors used 60% diatrizoate methylglucamine as the contrast agent. They have not had a single serious complication in 266 different cases, in 129 of which cerebrovascular disease was present.

Atherosclerotic disease of the vertebral-basilar arterial system is a common cause of symptoms due to cerebrovascular disease, comprising approximately one-third of the cases of stroke admitted to a general hospital if cerebral hemorrhage is excluded. Men and women are affected with approximately equal frequency, and the onset of symptoms commonly occurs in the 50's and 60's. Associated hypertension is extremely common. There are 5 principal sites of atherosclerotic changes of the vertebral-basilar system: (1) proximal portion of the vertebral artery at its origin from the subclavian artery; (2) cervical portion of the vertebral artery, commonly complicated by displacement of the vessel by exostoses and spur formation, due to cervical spondylosis; (3) intracranial portion of the vertebral artery; (4) basilar artery; and (5) posterior cerebral artery. The commonest site of involvement is the basilar artery. The disease process often involves several of these sites, and involvement is bilateral. The carotid arteries and their main branches also may show atherosclerotic involvement. Diffuse atherosclerosis of the basilar artery may result in occlusion of small branches of this vessel, and all that is apparent on angiography is dilatation and tortuosity of the basilar trunk. The majority of cases of atherosclerosis of the vertebral-basilar arterial system show diffuse involvement or lesions which are not amenable to surgical reconstruction by extracranial intervention.

Major arterial anomalies of the vertebral system occur in approximately 1 or 2% of persons, and must be considered in the interpretation of arteriographic studies. Such anomalies may play a part in the production of symptoms when another major vessel is occluded, since they provide little collateral blood flow. In the normal subject the contribution of blood from each vertebral artery remains separate and unmixed after entry into the basilar artery. As a result, partial or "half-filling" of the basilar artery may result if the vertebral artery is injected under low pressure. This may give rise to an artifactual impression of stenosis of the basilar artery. The vertebral-basilar system (via the posterior cerebral arteries) supplies the thalamus, peduncles, red nucleus, substantia nigra, and subthalamic nucleus, in addition to the brain stem and temporal and occipital lobes. Hence, "coma vigil" or akinetic mutism may occur, owing to thalamic ischemia. Rubral tremor, hemiballismus, hemichorea, tremor, and rigidity may result, owing to ischemia of the red nucleus, subthalamic nucleus, or substantia nigra.

Neuropathologic Review of Brain Lesions and Inherent Dangers of Chemopallidectomy: Report of a Case of Bilateral Pallidal Destruction. R. J. White, C. S. MacCarty and R. C. Bahn. A. M. A. Arch. Neurol. 2:12-18 (Jan.) 1960 [Chicago].

The tremor and rigidity of parkinsonism have been treated by the artificial production of lesions in or near the globus pallidus. The authors list the various methods by which these lesions have been produced, but give particular attention to chemopallidectomy. Because of the simplicity of Cooper's method, which utilizes pneumoencephalography and requires as special equipment only a peculiar catheter holder, the technique of chemopallidectomy could be performed by any neurosurgeon today, and might seem destined for universal application. However, although it apparently is used frequently, little information is available concerning (1) the location and extent of the lesion produced in the living brain and (2) the effect of the injected substance on brain tissue.

The authors present the history of a man who came to autopsy 2 months after he had been subjected to chemopallidectomy. Insertion of a catheter into the left globus pallidus resulted in apparent cessation of tremor and rigidity. A total of 0.4 ml. of Etopalin (8% solution of a specially prepared ethyl cellulose in 95% of alcohol) was injected in divided doses. At the completion of the procedure, painful stimulation did not produce tremor or rigidity on the right side. By the second postoperative day the patient's tremor had returned, and 2 days later a sudden elevation of temperature necessitated removal of the catheter, which was found encased with a firm solid substance, presumed to be the Etopalin and coagulated necrotic

Although a longer period of observation is necessary in the more recent cases, the reported data suggest that occult papillary carcinoma, with or without metastasis to the lymph nodes when first discovered, is an unusually curable disease. There are, in general, 2 main threats to life in papillary carcinoma of the thyroid, namely, local recurrence in the midline of the neck and distant metastasis, especially to the lung or bones. The good results with respect to local recurrence in these patients from the Mayo Clinic are understandable by virtue of the ease with which wide removal of the primary tumor may be accomplished. The complete absence of proved distant metastasis in this group, even in the patients with extremely bulky spread to lymph nodes, was an unexpected, but perhaps not too surprising, finding when the low incidence of such pread in papillary thyroid cancer of more conventional type is considered.

Multicentricity of Papillary Adenocarcinoma of the Thyroid: Influence on Treatment. B. M. Black, T. A. Kirk Jr. and L. B. Woolner. J. Clin. Endocrinol. 20:130-135 (Jan.) 1960 [Springfield, Ill.].

The authors report on 328 patients with papillary denocarcinoma of the thyroid gland, who were oprated on at the Mayo Clinic between 1940 and 954. Of these, 69 underwent unilateral subtotal obectomy; 50, bilateral subtotal lobectomy; 117, otal lobectomy; 82, total lobectomy and contraateral subtotal lobectomy; and 10, total thyroidecomy. Examination of the surgical specimens reealed multicentricity of papillary lesions in 5 (50%) f the 10 patients in whom total thyroidectomy was arried out, in 26 (18%) of the 142 patients from whom both lobes were removed partially or totally, nd in 39 (12%) of the total 328 cases. The 18% ncidence among the 142 patients is probably the est estimate of multicentricity provided by the athological findings alone. Of these 142 patients, t least one deposit was found in the opposite lobe f 17 (12%), and in each of these patients there was lso multicentricity in the lobe that harbored the linically evident primary lesion. These findings ustify the conclusion that papillary lesions are multicentric in at least 20% of cases. The multicenricity usually involves both lobes of the thyroid. One or more additional deposits of cancer may be xpected in the same lobe as the clinically evident rimary lesion in more than 10% of cases, and in he opposite lobe in a similar proportion of cases.

Further resection of the thyroid is advisable in atients in whom partial lobectomy or partial thyoidectomy has been carried out previously because f a nodule that subsequently proves to be a papilary lesion. The lymph nodes and node-bearing ascia should be removed cleanly from the tracheosophageal groove and from the region of the reurrent laryngeal nerve on the side of the obviously nvolved lobe in all patients. Preservation of a remnant of the thyroid on the apparently uninvolved side, together with the lymph nodes in the tracheoesophageal groove on that side, is justified in order to avoid total parathyroidectomy and, consequently, permanent tetany.

OPHTHALMOLOGY

Pulseless Disease, or Takayashu's Disease: Case Report. J. M. Pahwa, M. P. N. Pandey and D. P. Gupta. Brit. M. J. 2:1439-1442 (Dec. 26) 1959 [London].

A typical case of pulseless disease in a 27-year-old woman, the first such case reported from India, is described. Nearly a year and a half previously the patient had suffered from intermittent headaches on one side, and later after the headaches subsided had experienced frequent fainting attacks. On examination, she presented typical fundus changes, absent pulsation in the upper limbs, cataracts, attacks of syncope, and raised blood pressure in the lower limbs, with tendency to rise of ocular tension, probably due to new vessels and pigment deposits in the angle of the anterior chamber. The patient passed on to complete blindness, although the cataracts were removed successfully.

PATHOLOGY

Kaposi's Sarcoma and Myelogenous Leukemia. A. M. Abrahamsen and P. Wetteland. Nord. med. 62:1811-1813 (Dec. 17) 1959 (In Norwegian) [Stockholm].

Multiple hemorrhagic sarcoma (Kaposi's sarcoma) is relatively rare. Most of the patients are from northern Italy, Poland, Russia, and the equatorial parts of Africa. Fully 90% of the patients are men, and the age group from 40 to 80 years is especially affected. Early in the course there is an increased number of distended blood vessels, infiltration by lymphocytes, plasma cells, and fibroblasts, with small hemorrhages and blood pigment in the stroma. Vascular foci deep in the corium suggest Kaposi's sarcoma. The neoplastic lesions are distinguished by numerous groups of larger and smaller blood vessels, hemorrhages, and hemosiderin or are dominated by fibroblasts. The histological picture in a lesion can vary. Practically all organs can be affected. A cutaneous form affects legs, feet, hands, and nose, and in about 10% of the cases is combined with a visceral form especially localized in the gastrointestinal tract, liver, and lungs. A lymphonodular form may be localized to the retroperitoneal and mesenteric lymph nodes but can be generalized. An osseous form attacks the phalanges. Several localizations of the disease may be present in the same patient. The cutaneous form is radiosensitive, but new tumors often appear in new places. The average duration of life is from 5 to

These studies show that the parkinsonian tremor can be influenced from an area distant from the pyramidal system without impairment of voluntary movements. Further studies will have to ascertain to which extent these changes are caused by alterations in the activity of cell groups located in this region and to which extent they are related to fiber systems passing through it.

PEDIATRICS

Management of the Nephrotic Syndroma With Particular Reference to the Use of Triamcinolone. C. W. Daeschner, W. F. Dodge and L. L. Hill. J. Pediat. 56:48-60 (Jan.) 1960 [St. Louis].

The authors evaluated the results of triamcinolone therapy in 46 patients with the idiopathic nephrotic syndrome. In 19 of these patients further studies of their renal status were performed by percutaneous renal biopsy, and in 9 by renal hemodynamic measurements. Each patient was observed for a minimum of 3 days prior to the institution of steroid therapy and for the time that he was on a standardized diet containing less than 1 Gm. of sodium chloride per square meter of body surface area per day. Therapy with triamcinolone was begun in doses ranging from 40 to 70 mg. per square meter per day, given in 4 equal doses at 6-hour intervals. In the presence of an intercurrent infection, the triamcinolone dose was reduced to about twice the estimated physiological replacement level (8 to 12 mg. per square meter), and intensive antibiotic therapy was instituted. Therapeutic quantities of triamcinolone were continued until the patient's urine was entirely free of protein for 2 or 3 consecutive days or, in the presence of persistent proteinuria, for periods ranging from 22 to 28 days. The dose of triamcinolone was then reduced in an empiric, stepwise manner at 3-to-5-day intervals by increments of 2 mg. every 8 hours, and later 2 mg. every 12 hours. Prophylactic therapy was then instituted at a level of 20 to 30 mg. per square meter per day, given in 3 equally spaced doses on the same 3 consecutive days of each week, until no traces of proteinuria were found.

The best results were seen in 22 patients in whom the nephrotic syndrome had been present less than 4 months at the time treatment with triamcinolone was instituted and who had had no previous steroid treatment. Hypoproteinemia, hypercholesterolemia, massive proteinuria, edema, and good renal function were present in these patients. Their urine became free of protein after an average of 8 days of treatment with triamcinolone. Seven patients, however, showed a recurrence of nephrosis after the urine had been free of protein for longer periods; proteinuria was present in 5 of them, proteinuria and minimal edema in 1, and anasarca in 1. All these patients responded fairly promptly to therapy and were free of proteinuria after an average of 8 days of treatment. Six of 8 patients in whom onset of symptoms was present more than 4 months earlier, and who had not received adequate treatment prior to triamcinolone therapy, responded well to this therapy in an average of 8 days, with the loss of proteinuria and all other clinical and laboratory evidence of the nephrotic syndrome. One of these 8 patients was a failure, and in one edema cleared completely but trace amounts of proteinuria continued.

Twelve patients who had failed to respond to previous steroid treatment, and who had been known to have the nephrotic syndrome for an average of 33 months prior to the present period of treatment, received intensive therapy with triamcinolone. None of the patients became free of proteinuria at the end of therapy, although subsequent prophylactic treatment resulted in loss of proteinuria in 2 and loss of edema in 3 who hitherto were not free of it. In 4 patients the nephrotic syndrome had been present for 2 to 48 months at the time of their first steroid therapy and 12 to 61 months at the time of the present treatment, and all of them had a history of arterial hypertension. Treatment with triamcinolone was a failure in all 4 patients; 2 of them died. The authors found that prophylactic therapy in an interrupted fashion, when coupled with other anti-infection preventive measures, appeared to be satisfactory in most patients in the prevention of recurrence of nephrosis.

ENDOCRINOLOGY

Occult Papillary Carcinoma of the Thyroid Gland: A Study of 140 Cases Observed in a 30-Year Period. L. B. Woolner, M. L. Lemmon, O. H. Beahrs and others. J. Clin. Endocrinol. 20:89-105 (Jan.) 1960 [Springfield, Ill.].

The authors report on 140 patients with small or occult papillary carcinoma of the thyroid gland, who were treated surgically at the Mayo Clinic between 1926 and 1955. Of these, 58 (41%) had associated metastasis to the lymph nodes when first seen; 82 did not have lymph node metastasis, and their lesions were discovered incidentally at operations for a variety of other conditions of the thyroid gland. Of the 58 patients with metastasis, 4 died of causes unrelated to thyroid carcinoma, and 1 was lost to follow-up; 53 patients are alive and without evidence of carcinoma 3 to 32 years after operation. Of the 82 patients without metastasis, 11 died of causes other than thyroid carcinoma; 71 are living after periods ranging up to 30 years, and in none is either local or distant metastasis known to have occurred, although a few differences were noted. Histologically, no clear-cut line could be drawn between those lesions associated with metastasis to the lymph nodes and those discovered incidentally at operation for a variety of thyroid disorders.

Although a longer period of observation is necessary in the more recent cases, the reported data suggest that occult papillary carcinoma, with or without metastasis to the lymph nodes when first discovered, is an unusually curable disease. There are, in general, 2 main threats to life in papillary carcinoma of the thyroid, namely, local recurrence in the midline of the neck and distant metastasis, especially to the lung or bones. The good results with respect to local recurrence in these patients from the Mayo Clinic are understandable by virtue of the ease with which wide removal of the primary tumor may be accomplished. The complete absence of proved distant metastasis in this group, even in the patients with extremely bulky spread to lymph nodes, was an unexpected, but perhaps not too surprising, finding when the low incidence of such spread in papillary thyroid cancer of more conventional type is considered.

Multicentricity of **Papillary Adenocarcinoma of the Thyroid: Influence on Treatment.** B. M. Black, T. A. Kirk Jr. and L. B. Woolner. J. Clin. Endocrinol. 20:130-135 (Jan.) 1960 [Springfield, Ill.].

The authors report on 328 patients with papillary adenocarcinoma of the thyroid gland, who were operated on at the Mayo Clinic between 1940 and 1954. Of these, 69 underwent unilateral subtotal lobectomy; 50, bilateral subtotal lobectomy; 117, total lobectomy; 82, total lobectomy and contralateral subtotal lobectomy; and 10, total thyroidectomy. Examination of the surgical specimens revealed multicentricity of papillary lesions in 5 (50%) of the 10 patients in whom total thyroidectomy was carried out, in 26 (18%) of the 142 patients from whom both lobes were removed partially or totally, and in 39 (12%) of the total 328 cases. The 18% incidence among the 142 patients is probably the best estimate of multicentricity provided by the pathological findings alone. Of these 142 patients, at least one deposit was found in the opposite lobe of 17 (12%), and in each of these patients there was also multicentricity in the lobe that harbored the clinically evident primary lesion. These findings justify the conclusion that papillary lesions are multicentric in at least 20% of cases. The multicentricity usually involves both lobes of the thyroid. One or more additional deposits of cancer may be expected in the same lobe as the clinically evident primary lesion in more than 10% of cases, and in the opposite lobe in a similar proportion of cases.

Further resection of the thyroid is advisable in patients in whom partial lobectomy or partial thyroidectomy has been carried out previously because of a nodule that subsequently proves to be a papillary lesion. The lymph nodes and node-bearing fascia should be removed cleanly from the tracheoesophageal groove and from the region of the recurrent laryngeal nerve on the side of the obviously involved lobe in all patients. Preservation of a remnant of the thyroid on the apparently uninvolved side, together with the lymph nodes in the tracheoesophageal groove on that side, is justified in order to avoid total parathyroidectomy and, consequently, permanent tetany.

OPHTHALMOLOGY

Pulseless Disease, or Takayashu's Disease: Case Report. J. M. Pahwa, M. P. N. Pandey and D. P. Gupta. Brit. M. J. 2:1439-1442 (Dec. 26) 1959 [London].

A typical case of pulseless disease in a 27-year-old woman, the first such case reported from India, is described. Nearly a year and a half previously the patient had suffered from intermittent headaches on one side, and later after the headaches subsided had experienced frequent fainting attacks. On examination, she presented typical fundus changes, absent pulsation in the upper limbs, cataracts, attacks of syncope, and raised blood pressure in the lower limbs, with tendency to rise of ocular tension, probably due to new vessels and pigment deposits in the angle of the anterior chamber. The patient passed on to complete blindness, although the cataracts were removed successfully.

PATHOLOGY

Kaposi's Sarcoma and Myelogenous Leukemia. A. M. Abrahamsen and P. Wetteland. Nord. med. 62:1811-1813 (Dec. 17) 1959 (In Norwegian) [Stockholm].

Multiple hemorrhagic sarcoma (Kaposi's sarcoma) is relatively rare. Most of the patients are from northern Italy, Poland, Russia, and the equatorial parts of Africa. Fully 90% of the patients are men, and the age group from 40 to 80 years is especially affected. Early in the course there is an increased number of distended blood vessels, infiltration by lymphocytes, plasma cells, and fibroblasts, with small hemorrhages and blood pigment in the stroma. Vascular foci deep in the corium suggest Kaposi's sarcoma. The neoplastic lesions are distinguished by numerous groups of larger and smaller blood vessels, hemorrhages, and hemosiderin or are dominated by fibroblasts. The histological picture in a lesion can vary. Practically all organs can be affected. A cutaneous form affects legs, feet, hands, and nose, and in about 10% of the cases is combined with a visceral form especially localized in the gastrointestinal tract, liver, and lungs. A lymphonodular form may be localized to the retroperitoneal and mesenteric lymph nodes but can be generalized. An osseous form attacks the phalanges. Several localizations of the disease may be present in the same patient. The cutaneous form is radiosensitive, but new tumors often appear in new places. The average duration of life is from 5 to

10 years. Death is, as a rule, due to intercurrent infection, generalized visceral lesions, bleeding from internal organs, or complicating malignant lymphomas.

The authors report the case of a 78-year-old Scandinavian, with cutaneous and visceral manifestations of the disease, whose death 16 months after the first symptoms was due to melena and bronchopneumonia. Autopsy revealed Kaposi's sarcoma with involvement of skin, lungs, and colon. This man also had myelogenous leukemia, with hemorrhagic diathesis and infiltrations in bone marrow, spleen, liver, and kidneys. Myelogenous leukemia was previously observed in a case of Kaposi's sarcoma published by Tedeschi and associates.

Histochemical Studies in Cystic Fibrosis of the Pancreas. B. M. Wagner, G. J. Barbero, W. Chernick and H. S. Kim. A. M. A. J. Dis. Child. 99:61-66 (Jan.) 1960 [Chicago].

The authors performed postmortem examination, within 1 to 4 hours after death, on 6 children with cystic fibrosis of the pancreas in the Children's Hospital of Philadelphia. In addition to the histochemical studies of tissues obtained from these diseased children and of tissues from human controls, parallel observations were carried out in rabbits and kittens with the aid of chronic parasympathetic stimulation; the latter studies were based on the original claims of Farber that such stimulation could provoke pancreatic changes similar to cystic fibrosis. The results of the histochemical and immunochemical survey of intraluminal secretions of tissues of children who had died of cystic fibrosis showed that these secretions appeared to be strikingly similar to those noted in normal controls, with certain exceptions. The demonstration of metachromasia was apparently blocked by interfering proteins. In general, intraluminal secretions of the cystic fibrosis tissues contained more proteins than the tissues obtained from controls. Serum albumins and globulins were shown by immunofluorescent techniques. Attempts to reproduce the tissue changes consistent with cystic fibrosis in rabbits and kittens by the method of Farber were unsuccessful.

RADIOLOGY

Chest Roentgenographic Changes in Systemic Lupus Erythematosus. J. G. Bulgrin, E. L. Dubois and G. Jacobson. Radiology 74:42-49 (Jan.) 1960 [Syracuse, N. Y.].

Chest roentgenograms taken of 207 patients with lupus erythematosus were studied and compared with data from other studies. Ninety-six patients (46.5%) in this series showed no roentgenographic abnormalities, regardless of the duration of their disease. Eight of these patients came to autopsy, and there was no intrathoracic involvement except for strictly terminal phenomena, such as pulmonary edema or bronchopneumonia. Pleural changes only were found in 26 patients (12.6%); pleural and cardiac changes, in 34 (16.4%); pleural, cardiac, and pulmonary changes, in 6 (2.8%); and pleural and pulmonary changes, in 3 (1.4%). These figures are much lower than those found in studies by other investigators. Figures taken from the medical literature on the subject show a frequency of roentgenographic abnormalities which has varied from 67.7 to 100% of the patients observed, while in the series reported this frequency was only 53.5%. The extreme variability in incidence of abnormalities on chest roentgenograms in lupus erythematosus, as reported in the literature, is inexplicable. The authors' findings tend to confirm reports on the fibrinous nature of the pleural exudate and the impossibility of assigning a single cause of cardiac enlargement in any given case. Although it is unusual, systemic lupus erythematosus may exist for many years, and even terminate fatally, without any roentgenographically demonstrable thoracic abnormality.

Tumors of the Testis. R. G. Parker and J. B. Holyoke. Am. J. Roentgenol. 83:43-65 (Jan.) 1960 [Springfield, Ill.].

The authors report on 109 patients with a tentative diagnosis of testicular neoplasm, who were seen at the Swedish Hospital in Seattle between 1940 and 1955. Pathological material, including specimens of the primary tumor, was available from only 97 of the 109 patients. Forty-nine of the 97 patients had seminoma; 21, embryonal carcinoma; 19, teratocarcinoma; 2, choriocarcinoma; 3, interstitial-cell tumor; and 3, lymphoma. Both sides of the testes were involved with equal frequency for each tumor type. The average age of the patients with seminoma was 40 years; of those with embryonal carcinoma, 32 years; and of those with teratocarcinoma, 30 years. Surgery in these patients has virtually been limited to orchiectomy for removal of primary disease, while roentgenotherapy alone has been utilized in nearly all the patients for control of metastatic disease. Irradiation was not consistently directed to the pertinent lymphatics in adequate dosage during the period 1940-1949, whereas treatment during the period 1950-1955 was concise, and the irradiation dosage uniformly adequate by current standards. The results in the patients treated during the latter period have been better than in those treated between 1940 and 1949; however, evaluation remains difficult because of uncontrolled factors, such as the biased selection of material.

The survival rate in the total series was highest in patients with teratocarcinoma. The presence of a mature teratomatous component seems to be an indication of relative benignancy. No patient with

QUESTIONS AND ANSWERS

PHYSIOLOGICAL EFFECTS OF SNAKE VENOM

To the Editor:—*What is the physiological action of venom from the rattlesnake, the Ancistrodon contortrix (copperhead), and the Ancistrodon piscivorus (water moccasin)? Has acute renal failure ever been reported as a complication of bites from these snakes, and has renal dialysis been performed in patients with this particular complication?*

Gene H. Abels, M.D., Savannah, Ga.

Answer.—The most thorough recent review on the physiopharmacology and chemistry of Crotalidae venoms is that of Kaiser and Michl (Die Biochemie der tierischen Gifte, Franz Deuticke, Wien, 1958). Witham and associates (*Am. J. Physiol.* 173:535 [June] 1953) and Radomski and Deichmann (*Fed. Proc.*, vol. 16, no. 1, 1957) described certain of the cardiovascular effects of Crotalus venom, while Russell and associates (*Fed. Proc.*, vol. 19, no. 1, 1960) have developed several of the relationships between the cardiovascular effects and the changes produced in the respiratory and central nervous systems.

The vascular effects of the venom of the cottonmouth moccasin, Ancistrodon piscivorus, have been described by Fulton and associates. Hadidian described several of the zootoxicological effects of cottonmouth moccasin venom, and Minton and Deutsch and Diniz have written on some of the necrotizing and proteolytic effects of Crotalidae venoms. The fibrinolytic and coagulant activities of snake venoms have been demonstrated by Didisheim and Lewis.

Russell and Long, in the Second International Symposium on Myasthenia Gravis, described the changes at the neuromuscular junction that are produced by a number of venoms. Braganca reviewed several of the toxicological properties of snake venoms, particularly the effects of venom enzymes on nerve tissue. Radomski and Deichmann carefully pointed out the limitations in the relationships between the enzymes in certain venoms and specific toxicological activities.

Reports on renal complications after Crotalidae bites may be found in the papers cited in Harmon's and Pollard's bibliography on animal venoms (Gainesville, Fla., University of Florida Press, 1948). Renal lesions after the injection of Crotalus venom in monkeys have been described by Fidler and associates. Extensive clinical reports by Efrati and Reif and Russell are also of interest. Performance of "renal dialysis" in patients with this complication has not been reported in the literature.

Note: Complete bibliography of articles referred to will be supplied on request.

PRESCRIPTION FOR MIOTIC AND MYDRIATIC EFFECTS

To the Editor:—*Is there a good pharmaceutical preparation for administration to a patient with glaucoma and hypersensitivity of the carotid sinus, in whom miotic and mydriatic effects are desirable in the treatment of the respective conditions?* *M.D., Pennsylvania.*

Answer.—There is no good single pharmaceutical preparation for the treatment of a patient who has both glaucoma and hypersensitivity of the carotid sinus. A slight degree of continuing mydriatic effect might be obtained from use of tincture or extract of belladonna, in which the active principle, atropine, is well diluted by gums, waxes, rosins, and chlorophyll, which, by slowing its absorption, make its action mild and prolonged. Physostigmine salicylate or one of its synthetic derivatives may be added in minimal amounts to give the balanced effect desired.

TRICHINOSIS IN NONCARNIVOROUS ANIMALS

To the Editor:—*From time to time reference is made to the prevalence of trichinosis in animals in the arctic region. Included in this list are such herbivorous animals as the caribou and such fish-eaters as the walrus. What is the explanation for the occurrence of the infestation in these animals, since they do not eat the flesh of other mammals?* *M.D., Texas.*

Answer.—In arctic regions trichinae are most prevalent in the bear, the dog, and man. About half of the polar bears examined in one area were found to harbor these parasites, and in the sledge dog the incidence is even higher. With a high incidence in the bear, it is not difficult to understand the incidence in the dog and in man. As a matter of fact, serious outbreaks of trichinosis in natives have been reported in Greenland and traced to the consumption of meat from sledge dogs and polar bears.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

BOOK REVIEWS

Report of the First Institute on *Clinical Teaching: Report* of the Sixth Teaching Institute, Association of American Medical Colleges, Swampscott, Massachusetts, October 7-11, 1958. Edited by Helen Hofer Gee and Julius B. Richmond. With assistance of Planning Committee. Editorial coordination by E. Shepley Nourse. [Published also as part 2 of Journal of Medical Education, October 1959.] Cloth, $3; paper, $2. Pp. 233, with illustrations. Office of Director of Research, Association of American Medical Colleges, 2530 Ridge Ave., Evanston, Ill., 1959.

Previous institutes have been concerned with the teaching of basic sciences, the appraisal of applicants, and the ecology of the student. As in previous institutes, an appropriate pre-institute questionnaire was developed and the returns exhaustively analyzed for consideration by the invited participants during the three days of small group discussions, which ended with a final day's plenary session. The questionnaires for the Institute on Clinical Teaching were sent to deans, department heads of medical schools, clinical faculty personnel, institute participants, and hospital administrators. Most of the tables in this book are based on the analyses of this survey. Brief commentary on the samples, analytic techniques, and interpretation of the tables is also given in the appendix, along with some indication of future research planned on the basis of this information.

A total of 153 invited participants came from 85 medical schools in the United States, 11 in Canada, and 3 outside of North America, as well as persons from other university faculties, teaching hospitals, research institutes, foundations, and governmental agencies. In addition to medical men, representatives were invited from such disciplines as philosophy, law, economics, psychology, and sociology. In order to explore and discuss the issues facing clinical teachers in medical schools today, three broad topic areas were delineated with each topic allotted a day of discussion. These topics and their subcommittee chairmen were (1) the Objectives of Clinical Teaching, Dr. Stewart G. Wolf Jr.; (2) the Setting of Clinical Teaching, Dr. Charles Child III; and (3) the Student, the Patient, and the Teacher, Dr. Charles A. Joneway. The contents of the report are similarly organized. All the papers presented at the general sessions are reproduced in appropriate sections, and each part concludes with a review of the small group discussions by their chairmen. Part 4 contains papers by a philosopher, an economist, and a behavioral scientist; the papers were presented during a session devoted to viewing medicine and medical education from those viewpoints.

The entire report is important reading for all who are concerned with modern medical education from the clinical perspective. It represents a serious and thoughtful consideration of problems from a healthful diversity of viewpoints.

Glen R. Shepherd, M.D.

New and Nonofficial Drugs 1960: An Annual Compilation of Available Information on Drugs, Including Their Therapeutic, Prophylactic and Diagnostic Status, as Evaluated by the Council on Drugs of the American Medical Association. Cloth. $3.35. Pp. 768. J. B. Lippincott Company, E. Washington Sq., Philadelphia 5; 4865 Western Ave., Montreal 6, Canada, 1960.

The 1960 edition of this book, published annually since 1905, contains descriptions of more than 500 drugs based on appraisals by the Council on Drugs of the American Medical Association. In the preparation of this edition the Council obtained the opinions and advice of more than 250 authorities in the various fields of medicine and pharmacology. Monographs on 45 new agents have been added, whereas 21 descriptions of older drugs or those no longer commercially available have been omitted. New features include a listing of the year of introduction of each drug and an appendix of manufacturers.

Although there are brief chapter introductions summarizing the general properties of the various classes of pharmacological agents, this book is primarily a collection of short monographs on individual drugs. Pharmacological action, therapeutic uses, side-effects, toxicity, dosage, chemical formula, preparations, and trade names are described for each agent. The monographs are accurate, thorough, and objective. The candid presentation of undesirable as well as desirable characteristics of the drugs offers the physician a unique source of unbiased, critical information on most of the available newer compounds.

In the current edition, the Council's new policy, initiated in 1955, of providing information on all new drugs, whether established or not, is continued, so that inclusion of a drug in the book does not imply approval or endorsement by the Council. Hence, the selection or use of the drugs described must be decided on the basis of the information provided in each of the descriptive monographs. This work is strongly recommended to physicians, students and teachers of pharmacology, pharmacists, and to all who are interested in an authoritative source of information on drugs.

H. D. Kautz, M.D.

WASHINGTON NEWS

Self-Employed Retirement Bill . .
Competition in Drug Industry Noted . .
Forand Bill Developments . .
New Study of Drug Costs . .

SELF-EMPLOYED RETIREMENT BILL SLATED FOR ACTION

The way was paved for congressional action this year—barring unexpected developments—on legislation to encourage the self-employed to invest in retirement plans.

Chairman Harry F. Byrd (D., Va.) of the Senate Finance Committee said the Committee would take up the measure soon and that it probably would not be necessary to hold further hearings. Many senators have voiced support for the bill, which is aimed at giving self-employed persons such as physicians, dentists, farmers, lawyers, businessmen, and other persons in business for themselves similar tax treatment on retirement savings as is now granted salaried persons.

The House approved the bill last year, but the Senate Finance Committee did not vote on it after holding public hearings. At that time, the administration opposed it on the grounds that it would cost the Treasury about 365 million dollars in revenue. However, the Treasury Department recently proposed an alternative that would offer the self-employed about the same tax treatment as that contained in the House-passed Keogh-Simpson bill.

With the administration coming out in favor of the principle, odds appeared favorable that the legislation would clear Congress this year.

The bill before the committee would allow self-employed persons to defer taxes until the age of 65 years on up to 10% of their annual income (with a maximum of $2,500), if this were placed in a qualified retirement plan. The Treasury approach would be similar except that self-employed persons wishing to participate would have to establish retirement programs for their employees.

KEEN COMPETITION EXISTS IN DRUG INDUSTRY

Dr. Austin Smith, president of the Pharmaceutical Manufacturers Association, returned for another round of questioning before Senate investigators and declared that the facts brought out at previous sessions "prove a high degree of competition in the industry and disprove all arguments to the contrary."

Testifying before the Senate antitrust subcommittee headed by Sen. Estes Kefauver (D., Tenn.), Dr. Smith said that the drug industry embraces the concept of "total competition." "In fact, this competition is so keen that the drug industry has been severely criticized in this chamber for its vigor. Witnesses and others have claimed the industry is guilty of competitive excesses—in advertising, direct mail, sampling, and other sales methods.

"It seems to me that in their zeal to find fault with the drug industry some of our detractors are trying to have their cake and eat it too. The drug industry cannot be both too highly concentrated and also too competitive, for these are mutually exclusive concepts. Where the one exists the other is absent. You cannot conclude that this is a highly monopolistic industry."

Turning to a series of subcommittee lists of drugs discovered or developed in the United States and Europe, Dr. Smith said, "Frankly I am shocked by the attack on American research."

Distortion and misuse of figures were resorted to, he said, "in an effort to discredit the American achievements and to overrate the considerable achievements of our friends overseas." He added, "Yet even the subcommittee's own compilation—erroneous as it is—proves beyond doubt that American drug industry research has led the world in the past two decades."

He analyzed the committee lists to show that some of the drugs credited to European discoverers date back to the 16th and 17th centuries, and said, "A comparison of American drug progress, which hardly goes back more than 20 years, when stacked up against all the rest of the world for a period reaching back centuries before the American Revolution, is regarded by some as intended for only one purpose . . . to discredit the very real achievements that have transferred leadership in medical research from Europe to this country in the past generation. As a United States citizen I consider this unbecoming, to say the least.

"I think you have a right to know how incompetent these exhibits are," he said, adding, "Frankly, gentlemen, I find it incredible that such material can be seriously presented to a subcommittee of the United States Senate as straightforward fact.

"Of course the American industry is quick to bring foreign discoveries to this country for the benefit of our people," he asserted. "This is done in the public interest, openly. Nobody claims America has a monopoly on scientific savvy.

"The greatest tragedy in medicine is for a discovery to lie idle in a laboratory. The real boon to the world is getting a discovery developed, tested, and into the corner drugstore where it is available to save lives. This is a vital service to the American people. It reflects favorably upon the United States pharmaceutical industry."

LAWMAKERS MULL AGED HEALTH PLANS

The Ways and Means Committee, as of this writing, was still pondering what type of aged health measure, if any, to send to the floor of the House. As the lawmakers on the committee deliberated, House Speaker Sam Rayburn (D., Tex.),

(Continued on next page)

The bearded seal, the walrus, and even the whale have been found on occasions to be infested with trichinae. The only way these animals could have acquired the infestation was through the consumption of infected meat, presumably from polar bears and sledge dogs that somehow became available to them, or by eating their own kind. The caribou is, of course, not ordinarily a meat eater. Nevertheless, in the winter time, when other food is scarce, herbivorous animals will eat the flesh of other animals, including that of mammals. Field mice and other small mammals can also be a source of infestation for herbivorous and marine animals when eaten by them.

PASTEURIZED MILK

To the Editor:—*Which states in the United States have laws requiring that milk be pasteurized?*

John J. Clancy, M.D., Newington, Conn.

Answer.—A publication of the United States Department of Health, Education, and Welfare, Public Health Service, Division of Engineering Services, Milk and Food Program, entitled "List of States, Counties, and Municipalities in the U. S. Which Require Compulsory Pasteurization of Market Milk," names 11 states that require compulsory pasteurization of all or most of the milk sold within the state. These states are Arizona, Colorado, Delaware (except that sold by farmers to their tenants), Illinois, Indiana, Iowa (except grade A raw milk), Louisiana, Michigan (except six municipalities that voted otherwise), Minnesota, Nevada, and New York (in all incorporated communities of 10,000 population or more, except for certified or special grade A raw milk). Although it would appear that few states have legislative requirements for pasteurization of milk, the vast majority of municipalities in these states, and in the other states, have their own ordinances requiring the pasteurization of milk.

SKIN STRIAE

To the Editor:—*Of what significance are pale purple striae in the skin on the lateral aspect of the thigh of a 13-year-old girl? The striae are short, about 1 in. apart, and transverse to the long axis of the thigh. There is nothing unusual in this girl's medical history, except that she has done a moderate amount of ballet dancing. She has never been obese.*

Julia Baker, M.D., Mexico, D. F.

Answer.—Atrophic striae, or striae cutis distensae, are linear, atrophic lesions paralleling the lines of cleavage and grouped in a manner that suggests that the skin has been overstretched. If red or purple, they are probably new; they usually become white. They are permanent. While a mechanical cause of skin strain from stretching is not always apparent, the influence of this factor can seldom be excluded. The lesions frequently appear with a great change in the patient's weight, either an increase or a decrease; that they have occurred in a normal girl is unusual but not amazing, and their onset at puberty is rather common because of relation to rapidity of growth. According to the data submitted, the striae in this patient appear to be of no significance.

Editor's Note: In The Journal, Jan. 23, p. 392, is an abstract of an investigation of the "Histopathology of Striae Gravidarum" by L. O. S. Poidevin of London, England. He suggests a relationship between striae gravidarum and adrenal cortical hyperactivity.

TOLBUTAMIDE FOR ACNE

To the Editor:—*I would like information about tolbutamide, an antidiabetic drug said to be effective also for control of acne* (Canad. M. A. J. *80:629 [April 15], 1959).*

M. G. Radewan, M.D., Wenatchee, Wash.

Answer.—Unfortunately, there is no one drug which will control acne. Use of the so-called antidiabetic drugs has been advocated by some physicians as a useful adjunct in the treatment of chronic pustular acne; others have found the results disappointing. Experience with it is, at present, too limited for formulation of a final opinion.

CHRONIC DRAINING SINUS

To the Editor:—*The answer in* The Journal, *Dec. 19, 1959, page 2277, regarding a persistently draining sinus in a perineal wound after an abdominoperineal resection for carcinoma of the rectum outlines a course of investigation, including scout roentgenogram of the pelvis and subsequent injection of the perineal sinus with a radiopaque medium. I suggest that a pyelographic study would expand the scope of the diagnostic approach to include such frequent complications of this operation as ureteral injuries and ureteroperineal fistulas which extend into the posterior wall of the uterus.*

Robert E. Wilson, M.D.
1840 E. 18th St.
Denver.

The above comment was referred to the consultant who answered the original question, and his reply follows.—Ed.

To the Editor:—*I concur that "pyelography would expand the scope of the diagnostic approach" and should be performed if the diagnostic procedures suggested do not discover the origin of the sinus.*

PERSONNEL

Dr. John R. Heller, Director of the National Cancer Institute of the U. S. Public Health Service, was granted leave by the service to accept the presidency of the Sloan-Kettering Memorial Cancer Center in New York. Dr. Kenneth M. Endicott, formerly an associate director of the National Institutes of Health, was named to succeed Dr. Heller.

In other NIH changes, Dr. David E. Price, Chief of the Bureau of State Services, was appointed deputy director of NIH, a position which had been vacant since the retirement of Dr. Cassius J. Van Slyke last December. Succeeding Dr. Price as bureau chief was Dr. Theodore J. Bauer.

MISCELLANY

A House district subcommittee held sessions on legislation that would prohibit mail order drug houses from operating in the District of Columbia. Testifying in support of the measure, Dr. William S. Apple of the American Pharmaceutical Association declared that patients have to wait a week or 10 days to receive the drugs; "savings which were initially anticipated are never realized; the patient is exposed to unexpected expenses for additional medical care."

Legislation was introduced in the Senate by Sen. Hubert Humphrey (D., Minn.) to authorize a 10-year program of federal grants for construction of schools of veterinary medicine. The measure called for federal grants of 6 million dollars annually.

The American Medical Association supported legislation to provide a systematic procedure for the hospitalization of American nationals who are returned to this country because of mental illness. Such a bill must maintain the right of a citizen to the full protection of the law with respect to required judicial proceedings for hospitalization, the A. M. A. said.

The Public Health Service said that a preliminary check indicates that westerners are not absorbing more radioactive strontium (Sr^{90}) in their bones than other Americans. The tests are being conducted to determine whether westerners who live nearer nuclear test sites are exposed to significantly greater amounts of radioactivity than citizens in other parts of the country.

The federal government may have to pay cranberry growers and chicken farmers as much as 20 million dollars for losses suffered as a result of government crackdowns last year on tainted cranberry and chicken shipments. Payments would go to farmers who suffered losses through no fault of their own.

The Veterans Administration asked Congress for a 75-million-dollar first installment on its 12-year, 900-million-dollar hospital construction and modernization program. The request would finance the construction of three new hospitals, replacing older ones, and provide planning money for 18 buildings and modernization projects.

The HEW Department asked Congress to approve a bill establishing a new position of Administrative Assistant Secretary of Health, Education, and Welfare. The official, who would be paid $19,000 annually, would be responsible for department-wide management supervision.

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Lown, B., and Levine, S. A.:
Current Concepts in Digitalis Therapy, Boston,
Little, Brown & Company, 1954, p. 23, par. 2.

whose voice carries great weight in the House, declared he hoped that some sort of a compromise plan could be worked out without getting into the field of "socialized medicine."

Renewing his opposition to the Forand bill that calls for compulsory health care financing under the social security system, the House Speaker said he had not endorsed "any specific scheme" and that "various matters were being considered" by the Ways and Means Committee.

He made the statements in reply to a query from an individual physician about published reports that he had come out in favor of some type of social security health program.

Meanwhile, the American Dental Association vigorously opposed any compulsory health plan. In a statement filed with the Senate Labor Subcommittee on Aging, the Association said the Forand bill would establish "a drastic and irreversible system" of federally sponsored health care.

The Association said it was confident that there are ways of putting "adequate health care within reach of all those in need, including the needy aged, without resort to a system that we are sure will lead to a crippling of private professional practice and in turn to a lowering of general standards of health care."

INDUSTRY STUDIES COSTS OF MEDICAMENTS

The Pharmaceutical Manufacturers Association opened a sweeping study of the impact of the costs of medicaments on the American public. PMA President Dr. Austin Smith said the investigation will "bring together in one place information which has never been gathered in this country by any source, public or private."

Explaining the purpose of the study, Dr. Smith said, "It is widely stated by some that needed medication is not available because of financial difficulties. If this is true, it is time somebody lays out in the open the specific facts. Then, and only then, can specific remedies be discussed intelligently. If it is not true, the reasons for the confusion should be revealed."

Dr. Smith said that "for the first time, the efforts of all interested parties—manufacturers, members of the health team, public authorities, and patients themselves—will be united to study drug therapy and the results of their efforts will be disclosed for public examination."

The PMA planned to determine (1) the extent of use of prescription drugs by the general population; (2) the segments of the population that use drugs and under what circumstances; (3) the ways in which drugs are being provided in medical care programs; (4) whether needed drugs are not available to patients; (5) which elements, if any, of the population may be deprived of necessary drug therapy and the reasons for such deprivation if it exists, and (6) the true relationship of prescription drugs to medical care needs and costs.

Dr. Smith said representatives of consumer groups and various members of the health team will be asked to assist in the study with a special industry group, whose membership will be announced shortly.

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APRIL 30, 1960

EMPHYSEMA, SOOT, AND PULMONARY CIRCULATION—MACROSCOPIC STUDIES OF AGING LUNGS

Charles P. Oderr, M.D., New Orleans

Two hundred lungs, obtained from persons dying of diseases other than pulmonary tuberculosis, were fixed in the inflated state to permit study of the relation between emphysema and deposits of soot. The evidence showed that chronic emphysema usually develops first in small areas of trapped parenchymal soot deposits; it is manifested by abnormal fenestrations in the interalveolar septums and by increased diameter of the alveolar ducts. The emphysema accompanying deposits of soot can be explained as resulting from tissue defects and disarrayed mechanical forces. Precapillary vessels are found protruding into the air spaces at the alveolar duct level, providing a possible mechanism for correlation between aerodynamics and hydrodynamics in the lung parenchyma. The morphologic basis for an extensive semishunt mechanism is demonstrated in the periphery of each lobe.

THE porous nature of lung tissue affords an unusual opportunity for macroscopic study if one first fixes the intact lung in the inflated state.[1] This can be done with luid fixative under appropriate pressure or with air blown through the main bronchus at a similar pressure level. Slices through the entire lung, cut rom 0.5 to 1 cm. in thickness, are suitable for various kinds of macroscopic study. With use of his approach I have found a correlation between parenchymal soot deposit and emphysema and have observed important details regarding the vascular pattern.

Preparation of Material

Our material has consisted mainly of 200 human ungs obtained from the morgue of an adult general hospital. The cases represented a fair cross section of patients dying of diseases other than pulmonary uberculosis and primary pulmonary neoplasm. Most of the cases were prepared by the air inflation echnique, since this affords the greatest opportunity or versatility in methods of macroscopic study. This method is also suited to handling fairly large quantities of material. The main bronchus is cut as close o the carina as possible. A piece of 0.25-in. rubber ubing (inside diameter) is inserted into the bronchus and secured in place with heavy string. About 50 cc. of 95% alcohol is usually introduced into the bronchus to reduce bacterial activity. The lung is connected through one arm of a Y-tube to an air line and through the other arm to a manometer. The air valve is opened slowly, and the lung is allowed to inflate at a pressure not exceeding 25 to

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Chief, Radiology Service, Veterans Administration Hospital, and Associate Professor of Medicine (Radiology), Tulane University School of Medicine.

MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. F. J. L. Blasingame, 535 North Dearborn St., Chicago 10, Executive Vice-President.

1960 Annual Meeting, Miami Beach, Fla., June 13-17.
1960 Clinical Meeting, *Washington, D. C.*, Nov. 28-Dec. 1.
1961 Annual Meeting, New York City, June 26-30.
1961 Clinical Meeting, Denver, Nov. 27-30.
1962 Annual Meeting, Chicago, June 11-15.
1962 Clinical Meeting, Los Angeles, Nov. 26-29.

AMERICAN

1960

April

American Academy of Neurology, Eden Roc Hotel, Miami, Fla., Apr. 25-30. Mrs. J. C. McKinley, 4307 E. 50th St., Minneapolis 17, Executive Secretary.

American Association of Pathologists and Bacteriologists, Hotel Peabody, Memphis, Tenn., Apr. 28-30. Dr. Russell L. Holman, Dept. of Pathology, L. S. U. School of Medicine, New Orleans, La., Secretary.

American College Health Association, *Toronto, Canada*, Apr. 27-30. Dr. Norman S. Moore, Cornell University, Gannett Clinic, Ithaca, N. Y., Secretary Treasurer.

North Dakota State Medical Association, Dacotah Hotel, Grand Forks, Apr. 30-May 3. Mr. Lyle A. Limond, Box 1198, Bismarck, N. D., Executive Secretary.

Southeastern Dermatological Association, Nashville, Tenn., Apr. 30-May 1. Dr. Robert N. Buchanan Jr., 706 Church St., Nashville, Tenn., Organizing Physician.

May

Academy of Psychoanalysis, Hotel Claridge, Atlantic City, N. J., May 7-8. Dr. Joseph H. Merin, 125 E. 65th St., New York 21, Secretary.

Aerospace Medical Association, Americana Hotel, Bal Harbour, Fla., May 9-11. Dr. William J. Kennard, Aerospace Medical Association, Washington Natl. Airport, Washington 1, D. C., Secretary-Treasurer.

American Association for Cleft Palate Rehabilitation, Brown Palace Hotel, Denver, May 12-14. D. C. Spriestersbach, Ph.D., University Hospitals, Iowa City, Iowa, Secretary-Treasurer.

American Association of Genito-Urinary Surgeons, Dearborn Inn, Dearborn, Mich., May 11-13. Dr. William J. Engel, 2020 E. 93rd St., Cleveland 6, Secretary.

American Association on Mental Deficiency, Lord Baltimore Hotel, Baltimore, May 16-21. Mr. Neil A. Dayton, P. O. Box 51, Mansfield Depot, Conn., Executive Secretary-Treasurer.

American Association of Plastic Surgeons, Milwaukee Inn, Milwaukee, May 17-20. Dr. Thomas D. Cronin, 6615 Travis St., Houston 25, Texas, Secretary.

American Association for Thoracic Surgery, Deauville Hotel, Miami Beach, Fla., May 11-13. Dr. Hiram T. Langston, 7730 Carondelet Ave., St. Louis 5, Secretary.

American College of Cardiology, Indianapolis, May. Dr. Philip Reichert, 2709 Empire State Bldg., New York 1, Executive Director.

American Federation for Clinical Research, Chalfonte-Haddon Hall, Atlantic City, N. J., May 1. Mr. James E. Bryan, 250 W. 57th St., New York 19, Executive Secretary.

American Gynecological Society, Williamsburg Inn, Williamsburg, Va., May 30-June 1. Dr. Andrew A. Marchetti, Georgetown Univ. Hosp., Washington 7, D. C., Secretary.

American Ophthalmological Society, The Broadmoor, Colorado Springs, Colo., May 16-18. Dr. Maynard C. Wheeler, 30 W. 59th St., New York 19, Secretary.

American Orthopaedic Association, The Homestead, Hot Springs, Va., May 30-June 2. Dr. Lee Ramsay Straub, 535 E. 70 St., New York 21, Secretary.

American Pediatric Society, New Ocean House, Swampscott, Mass., May 5-6. Dr. Aims C. McGuinness, 2800 Quebec St., N. W., Washington 8, D. C., Secretary-Treasurer.

American Psychiatric Association, Inc., Hotel Traymore, Atlantic City, N. J., May 9-13. Dr. C. H. Hardin Branch, 156 Westminster Ave., Salt Lake City 15, Utah, Secretary.

American Psychoanalytic Association, Chalfonte-Haddon Hall, Atlantic City, N. J., May 6-9. Mrs. Helen Fischer, One E. 57th St., New York 22, Acting Executive Secretary.

American Society for Clinical Investigation, Haddon Hall, Atlantic City, N. J., May 1-2. Dr. Saul J. Farber, N. Y. U. College of Medicine, 550 First Ave., New York 16, Secretary.

American Trudeau Society, Statler and Biltmore Hotels, Los Angeles, May 16-18. Mr. Frank W. Webster, 1790 Broadway, New York 19, Executive Secretary.

American Urological Association, Inc., The Palmer House, Chicago, May 16-19. Mr. William P. Didusch, 1120 N. Charles St., Baltimore 1, Executive Secretary.

Arizona Medical Association, Inc., Safari Hotel, Scottsdale, Ariz., May 4-7. Mr. Robert Carpenter, 1021 Central Towers Bldg., Phoenix, Ariz., Executive Secretary.

Association of American Physicians, Haddon Hall, Atlantic City, N. J., May 3-4. Dr. Paul B. Beeson, Yale Univ. School of Medicine, New Haven 11, Conn., Secretary.

Association of Surgeons of the Southern Railway System, Charleston, S. C., May 9-10. Dr. Rudolph M. Landry, 707 Walnut St., Chattanooga 2, Tenn., Program Chairman.

Georgia, Medical Association of, Columbus, May 1-4. Mr. Milton D Krueger, 938 Peachtree St., N. E., Atlanta 9, Ga., Executive Secretar

Hawaii Medical Association, Honolulu, May 12-15. Mr. Lee McCalli 510 S. Beretania St., Room 200, Honolulu 13, Hawaii.

Illinois State Medical Society, Hotel Sherman, Chicago, May 24-2 Dr. George F. Lull, 185 N. Wabash, Chicago, Secretary.

Kansas Medical Society, Baker Hotel, Hutchinson, May 2-5. Mr. Oli E. Ebel, 315 W. Fourth, Topeka, Kan., Executive Secretary.

Louisiana State Medical Society, Capitol House, Baton Rouge, M 2-4. Dr. C. Grenes Cole, 1430 Tulane Ave., New Orleans 12, Secreta Treasurer.

Massachusetts Medical Society, Statler-Hilton Hotel, Boston, May 1 19. Mr. Everett R. Spencer Jr., 22 The Fenway, Boston 15, Director Public Relations and Administration.

Medical Library Association, Inc., Muehlebach Hotel, Kansas C Mo., May 16-20. Miss Nettie A. Mehne, Upjohn Company Libr 301 Henrietta St., Kalamazoo, Mich., Secretary.

Minnesota State Medical Association, Kahler Hotel, Rochester, M 23-25. Mr. Harold W. Brunn, 496 Lowry Medical Arts Bldg., St. Pau Executive Secretary.

Mississippi State Medical Association, Hotel Heidelberg, Jackson, 10-12. Mr. Rowland B. Kennedy, P. O. Box 4606, Fondren Stat Jackson, Miss., Executive Secretary.

National Tuberculosis Association, Statler & Biltmore Hotels, Angeles, May 15-20. Mr. James G. Stone, 1790 Broadway, New 19, Executive Secretary.

Nevada Academy of General Practice, Reno, May 12-14. Dr. Re Peters, 475 S. Arlington Ave., Reno, Nev., Program Chairman.

New Jersey, Medical Society of, Chalfonte-Haddon Hall, Atlantic May 14-18. Mr. Richard I. Nevin, P. O. Box 904, Trenton 5, Executive Officer.

New Mexico Medical Society, Western Skies Hotel, Albuquerque, 10-13. Mr. Ralph R. Marshall, 220 First National Bank, Albuque N. M., Executive Secretary.

New York, Medical Society of the State of, Statler-Hilton New York City, May 7-13. Dr. Herbert T. Wagner, 750 3rd Ave., York 17, Executive Director.

North Carolina Medical Society, Hotel Sir Walter, Raleigh, May 7-11. Mr. James T. Barnes, Capital Club Bldg., Raleigh, N. C., Executive Secretary.

Ogden Surgical Society, Ogden, Utah, May 18-20. Dr. D. E. Gra 412 First Security Bank Bldg., Ogden, Utah, Secretary.

Ohio State Medical Association, Sheraton Cleveland, Cleveland, Ma 17-19. Mr. Charles S. Nelson, 79 E. State St., Columbus 15, Exec tive Secretary.

Oklahoma State Medical Association, Oklahoma City, May 1-4. M R. H. Graham, 601 N. W. Expressway, Oklahoma City, Okla., Executi *Secretary.*

Rare Earths in Biochemical and Medical Research Conferen Iowa State University, Ames, Iowa, May 11-13. J. G. Graca, Ph.D., Co lege of Veterinary Medicine, I. S. U., Ames, Iowa, *Program Chairma*

Rhode Island Medical Society, May 10-11. Dr. Arthur E. Hard 2 Post Rd., Warwick 5, R. I., Secretary.

Society of American Bacteriologists, Bellevue-Stratford Hotel, Phi delphia, May 1-5. Dr. E. M. Foster, 311 Bacteriology, U. of Wiscons Madison 6, *Secretary.*

Society of Pediatric Research, New Ocean House, Swampscott, Ma May 3-5. Dr. Clark D. West, The Children's Hospital, Cincinnati Secretary.

South Carolina Medical Association, Ocean Forest Hotel, My Beach, May 17-19. Mr. M. L. Meadors, 309 W. Evans St., Floren S. C., Executive Secretary.

South Dakota State Medical Association, Alonzo Ward Hotel, Al deen, May 14-17. Mr. John C. Foster, 300 First Natl. Bank Bl Sioux Falls, S. D., Executive Secretary.

Student American Medical Association, *Statler-Hilton* Hotel, Angeles, May 5-8. Mr. R. F. Staudacher, 430 N. Michigan, Chicago Executive Director.

Symposium on the Psychological and Physiological Aspects Space Flight, Southwest Research Institute, Hilton Hotel, Antonio, Texas, May 26-27. For information write Mr. Jack Har 8500 Culebra Rd., San Antonio 6, Tex., Public Relations Dir

Virginia Academy of General Practice, Virginia Beach. For infor tion write: Virginia Acad. of General Practice, 4205 Dover Rd., mond 21, Va.

Wisconsin, State Medical Society of, Hotel Schroeder, Milwa May 3-5. Mr. C. H. Crownhart, 330 E. Lakeside St., Madison 5, Secretary.

June

American Academy of Tuberculosis Physicians, Miami Beach, June 11. Dr. George P. Bailey, P. O. Box 7011, Denver 6, Secreta

American College of Angiology, Roney Plaza Hotel, Miami B Fla., June 10-12. Alfred Halpern, Ph.D., 11 Hampton Court, Neck, N. Y., Executive Secretary.

American College of Chest Physicians, Miami Beach, Fla., June Mr. Murray Kornfeld, 112 E. Chestnut St., Chicago 11, Exe *Director.*

American Diabetes Association, Inc., Hotel Deauville, Miami Fla., June 11-12. Mr. J. Richard Connelly, 1 E. 45th St., New York Executive Director.

American Electroencephalographic Society, Belmont Hotel, Ca Cod, Mass., June 10-12. Dr. George A. Ulett, 1420 Grattan St., S Louis 4, Secretary.

(Continued on page 26)

lar septum (fig. 3 and 4). The important implica-ions of a wound in this position are as follows: 1. It is present in tissue which is in almost constant notion and is periodically put under more or less ension. 2. Since the tissue is a thin septum, the

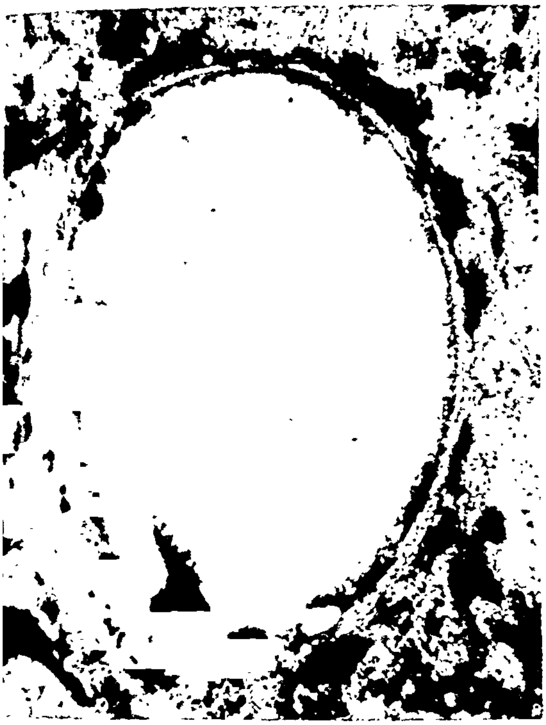

Fig. 3.—"Wound" in emphysematous interalveolar septum ich contains numerous small soot deposits. Fenestration surrounded by an elastic fiber. Photograph of dissected- septum from dry-inflation fixed lung (± × 140).

ound is likely to be a fistula. Such fistulas are ınd in large numbers in the lungs of older adults at come to autopsy. Enlargement of the air sacs iich suffer nonhealing septal "wounds" occurs nd in hand with enlargement of the "wound" itself. l degrees of enlargement of the "wound" can be monstrated in macroscopic studies, up to the point iere two air sacs could be said to have coalesced.

The other tissue lesion, observed at the macro-pic level, in the common variety of chronic nphysema bears a similarity to the principal lesion coal miner's (coal dust) disease. This lesion is servable as an increased diameter of the alveolar ct. The actual measurement being made is the ameter of the helix made by the spiral smooth isculature which forms the structural basis for e (involved) alveolar ducts (fig. 5 and 6). (Contigu-s ductal structures may also be involved; proxi-lly, there are the much less numerous respiratory onchioles; distally, there are the numerous atria d sacculi in which elastic bands appear to take the ice of spiral smooth muscle.) The diameters of the olved alveolar ducts enlarge at the expense of e alveoli, which form the baffle-like lining of the lls of the ducts (fig. 5). Soot particles tend to pile up behind these spiral muscles, the proper "tonus" of which protects the baffle-like alveolar structure. There is also apparent elongation of the alveolar ducts, but this has been much more difficult to evaluate.

There is one observation regarding the inflation and deflation of freshly removed lungs, with visible bullae, which is of particular significance. I have noted, when inflating such a lung, that emphysematous bullae tend to fill before surrounding normal lung, and that they tend to empty after the surrounding normal lung. Similar findings have been observed by Dayman [4] in similar preparations, and by Head and Avery [5] during thoracoscopy, performed with the thorascope inside bulla. I have not found any valve-like lesions in respiratory bronchioles which might explain such a phenomenon. However, localized loss of "tissue tension" ("tissue tension" might be more fully described as a three-dimensional geodesic pattern of balanced tension lines) can be inferred from the parenchymal tissue defects described above. This can be as effective as a valve in producing air flow resistance, as will be discussed later.

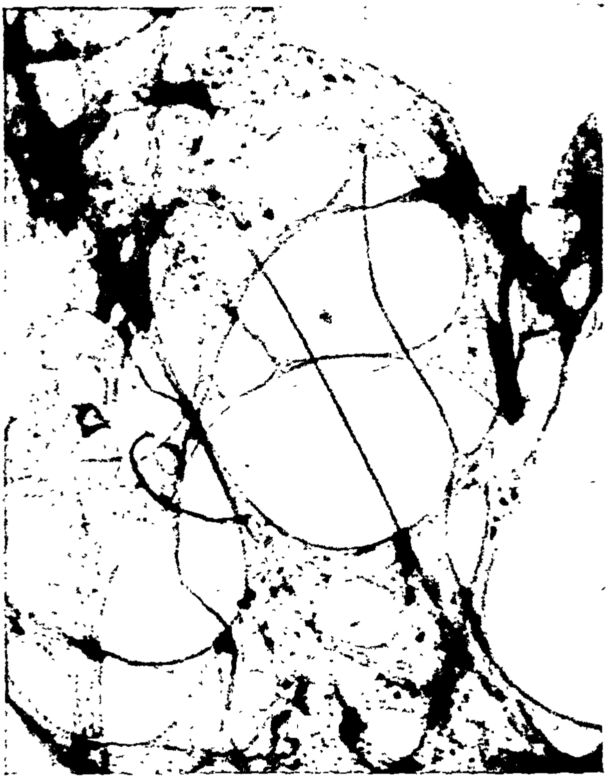

Fig. 4.—Interalveolar septal "wounds" of various sizes, some in areas of soot deposit and some not. Photograph of dissected-out septum from dry-inflation fixed lung (× 67).

Pulmonary Vasculature (Normal Lungs)

Macroscopic methods have revealed two details of the vascular pattern which seem to be important. The first one was revealed when the thicker slices

30 cc. of water. When air flow is maintained at this pressure for four or five days, most lungs will be fully dried out, without necrosis, and will remain in the inflated state. They can then be preserved for long periods in ordinary cardboard boxes containing a few crystals of paradichlorbenzene. Slices of desired thickness are made by means of an electric meat cutter. Twenty lungs of dogs, obtained from a veterinary morgue, were processed by a similar method.

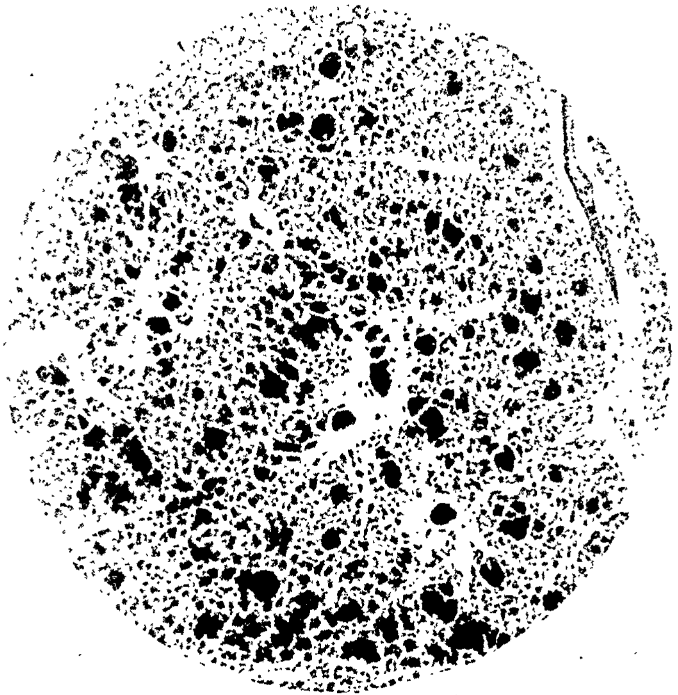

Fig. 1.—Contact microradiogram of 0.5-mm. lung slice (from patient aged 42 years). At kilovoltage used (1.6 kvp), the soot appears as densities surrounding enlarged lumina of alveolar ducts and compromising integrity of alveoli lining walls of ducts. Such lesions are believed to represent early stage in common type of chronic emphysema (× 7).

The method of fluid fixation under pressure is of recent origin. Its disadvantages are as follows: 1. It is more time consuming. 2. The bulk and weight of the material make it difficult to handle a large number of cases. 3. Thin slices are more difficult to obtain. 4. Some methods of macroscopic study (especially radiographic methods) are not usable. However, it provides a valuable check on the dry-fixing method and has already contributed new findings regarding precapillary vessels. The handling of the wet material can be facilitated by sealing the slices in separate plastic envelopes. The method used for maintaining fluid-fixative pressure has been described by Heard.[2] This method consists of maintaining proper hydrostatic pressure (25 cm. H_2O) by recirculating the fluid fixative which leaks out of the lung. Even at very low pressures, fluid (or air) introduced into the main bronchus leaks out of the lung in various ways, but chiefly through the vessels. The communication points in the parenchyma for this "leakage" are evidently of exceedingly small size and, so far, have escaped our visual detection. Heard, and Askewald (of Oslo) have described, in verbal communications, a simplified formalin inflation method with use of a vat attached to a mechanical evacuating pump.

Emphysema and Soot

In the material here presented deposition of soot in the parenchyma is strongly correlated with areas of emphysema (fig. 1). The area of soot deposit frequently extends beyond the areas of developed emphysema. In the visceral pleura (fig. 2) soot tends to collect in areas of lesse support, i. e., subjacent to intercostal spaces[3] (including the apex) rather than under the ribs, an subjacent to the superior vena cava rather than t the aorta or the innominate arteries. There is always soot in the lung subjacent to pleural soo Emphysema develops in many of these lung are but seldom develops when there is no soot deposi In the more central areas of the lung soot depos associated with emphysema, or even soot-free emphysema, will sometimes be found in "kissin areas" of two secondary lobules, with the remainder of the lobules normal. The examination of th canine lungs provided interesting negative findings. Despite the fact that the dogs examined w city dogs, their lungs were virtually free from a grossly visible parenchymal soot deposits, and t were likewise virtually free from emphysema.

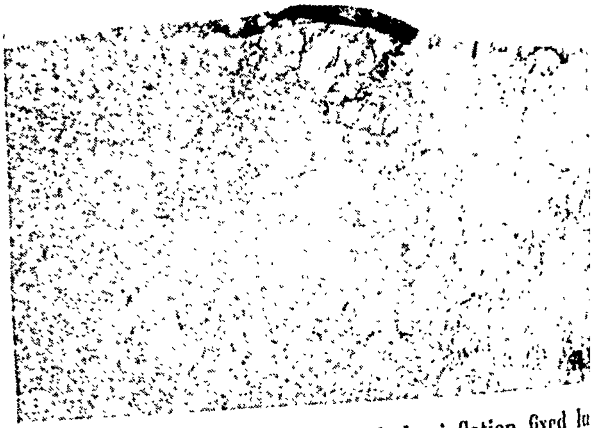

Fig. 2.—Two-millimeter slice of dry-inflation fixed lu photographed by transmitted light. Soot is shown accum lating in pleura and subjacent lung in area of lesser ch wall support. Emphysema is developing in subjacent lu (× 4.5).

I have been impressed by two kinds of tis lesions at the macroscopic level. One of these see to be in the nature of a tissue "wound" in the alv n (the more centrally located) respiratory bronchi-les. The study on dogs that showed neither paren-hymal soot nor emphysema would appear to lend upporting evidence to a soot-emphysema relation-hip. It would therefore be of great interest to study uman lungs by a total-slice method, in non-soot-olluted regions.

The tissue "wounds" that were observed to form nteralveolar fistulas may, in the early stages, furnish athways of useful collateral air circulation; how-ver, when their number and size become excessive, ollateral circulation" turns out to be a shuttling ack and forth of "dead" air. These things may not revent healing of the "wound" under favorable onditions of health and youth, but probably do nterfere with the rapid healing necessary to prevent reparable enlargement under less favorable condi-ons of tissue vigor. As far back as 1936 Macklin[7] ggested that excessive pore formation might rep-sent early emphysema.

One mechanism by which soot could produce a sue wound is suggested by the work of Lawther d Waller[8] of St. Bartholomew's Hospital, Lon- n. They found that certain soot particles trap id radicles internally. When these particles are llected on cascade impactor slides coated with latin films containing a color indicator, a strongly d reaction is observed. Many other mechanisms ve been suggested by which air-polluting inhal- s could generate structural and functional ab-rmalities in the lung. Some of these are discussed the Proceedings of the National Conference on Pollution.[9]

The second observation classed as tissue injury is increased diameter of the alveolar ducts. This uld seem to be the result of elongation of the ral musculature. It is possible that this is due to of tonus, which is brought about in some way the soot which accumulates adjacent to it. How-r, as with alveolar septal defects, soot action is bably only one link in a chain of factors which significant in bringing about the tissue insult. e increased volume of the ductus must be classed n increase in "dead space." It is true that part of increased volume (that part due to elongation the ductus) could be unrelated to lost muscle us and be merely the result of a stretching out he spiral in the manner in which an accordion ngates. We think of the accordion effect as the ncipal mode of volume change resulting from phragmatic and chest wall action. One might sider this the extrinsic factor in emphysema in trast to the intrinsic factor of tissue pathology he lung itself.

he manner by which these two lung tissue in-es (excessive fistula formation and lost smooth scle "tonus," or its equivalent) bring about in-sing impairment of mechanical exchange of ses is thought to be probably as follows: The tissue injuries result in structural alterations, which change the ratio of inflow resistance to outflow resistance. To avoid being confused about this, it is well to imagine starting with a completely collapsed lung. The diseased (emphysematous) areas are then more readily filled than normal areas. But, after the original filling, emphysematous areas are both less easily emptied, and less easily filled with fresh air, than are normal areas. The increased resistance to inflow is the result of the excessive residual air. The trapped residual air has not only effaced the decreased resistance of the diseased tissue but has gone on to establish an increased resistance as compared to surrounding normal tissue.

The increased resistance to outflow is the result of a combination of events which may be superimposed on bronchiole pathology but do not necessarily depend on it. The basic principles are well explained and illustrated by Dayman[4]; my associates and I previously described[1c] a model in which an area of lost tissue tension (emphysema area) was represented by a balloon with several small holes in it. With this model in mind, it is easy to understand why a slow, carefully controlled expiration permits better emptying of bullous and emphysematous areas than is possible with a rapid and forceful expiratory effort. Whether, during such

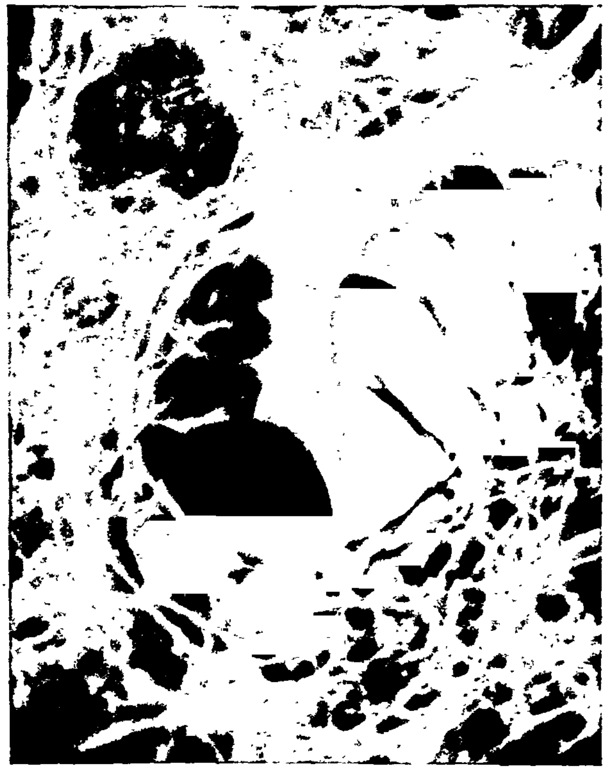

Fig. 6.—Microradiogram (3.5 kvp) of alveolar duct in slice of dry-inflation fixed lung ± 0.48 mm. thick. Note spiral structure and small vessel coursing along ductus (± × 120).

of dry-fixed lungs were radiographed with extremely soft x-rays. The pattern consisted of a peripheral zone in each lobe in which the small vessel network was much denser than elsewhere. The arterioles and corresponding venules were more closely approximated than in the central portion of the lobes (fig. 7). The capillary path for blood reaching this peripheral zone would seem to be much shorter. Pritchard and co-workers [6] have shown, in physiological studies, that organs with hilar-type structure demonstrate peripheral vascular phenomena that are different from the remainder of the organ. For example, in the kidney they demonstrated peripheral ischemia by angiography (in a living anesthetized animal) and peripheral hypervascularity with roentgenograms of the same organ by opaque injection of its vessels immediately post mortem. They showed a similar peripheral ischemia in the lung by angiogram but not the hypervascularity phase. The "soft x-ray" roentgenograms of the resected lung with retained blood correspond to the roentgenograms of the resected and injected kidneys.

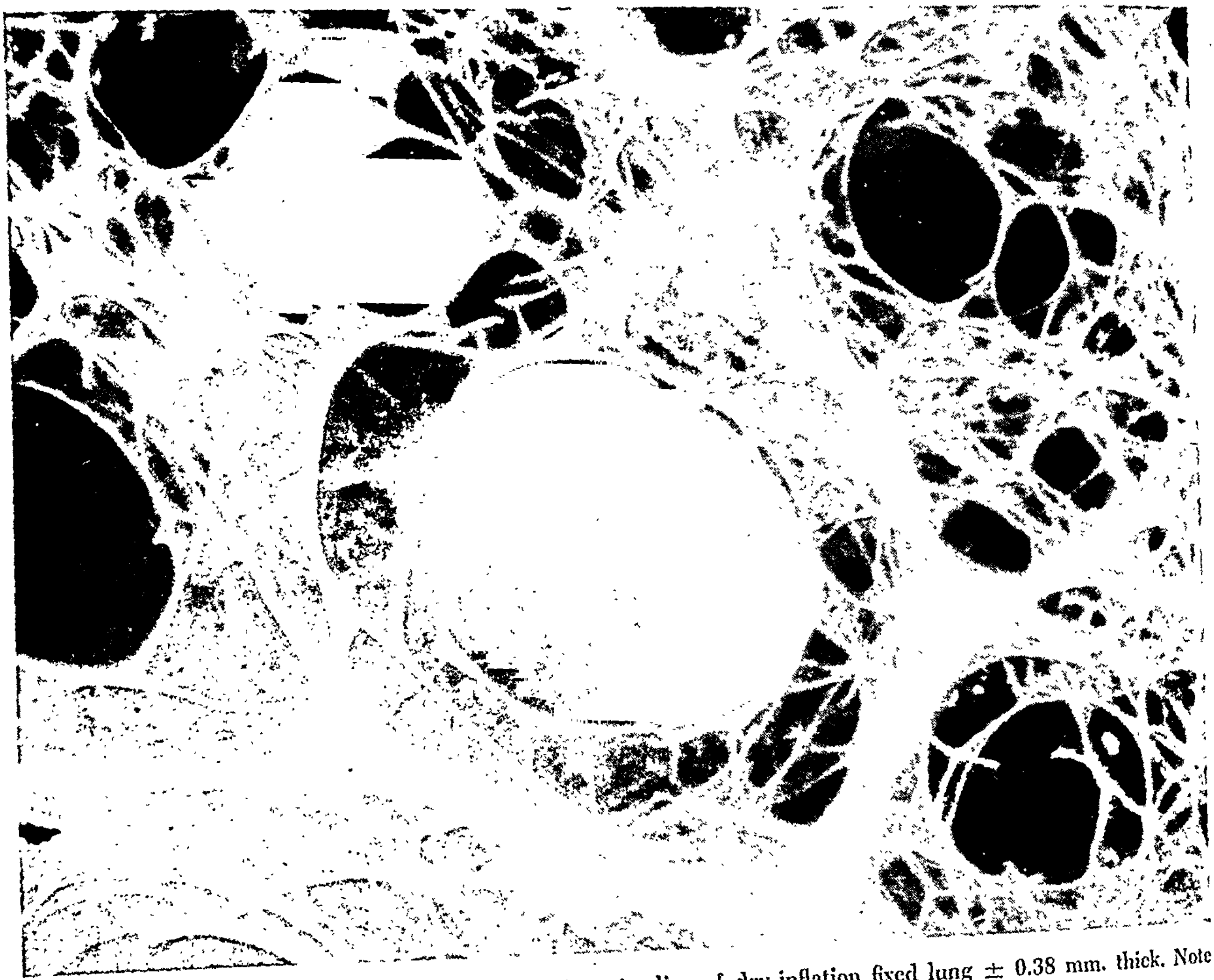

Fig. 5.—Microradiogram (3.5 kvp) of alveolar ducts in slice of dry-inflation fixed lung ± 0.38 mm. thick. Note spiral structure of ducts and alcove-like structure of alveoli (± × 120).

The second significant detail of the vascular pattern was revealed in dissecting specimens for microscope studies of the thinner and undried slices of lung. The lungs for this study had been fixed with Orth's solution under 25 cm. of water pressure. When alveolar ducts had been cut across at certain levels of their structure, vessels of a precapillary size could be seen projecting into the lumen of the air passage, as they passed over the ridge of a spiral muscle (fig. 8 and 9). One finds these vessels passing over only a small percentage of the spiral-muscle ridges of any given alveolar duct.

Comment

The findings presented here seem to indicate that the common form of chronic emphysema begins in highly localized areas, probably comprising only one or a few alveolar ducts with their accompanying air sacs. In this material, early areas tended to be in the pathways trapping soot particles. A point which lends weight to the view that soot is present before the emphysema is the tendency for the area of soot deposit in the parenchyma to be found beyond the limits of the localized emphysema. One gets the impression that the disease process is "invading" the soot-laden areas. The finding of soot and early emphysema in peripheral "kissing areas" of adjacent secondary lobules would seem to indicate that the crucial factor is *local* and in the peripheral part of the secondary lobules rather than emands and partly on the degree of health or sease existing in the central parts of the pulmo- ry lobes.

Summary and Conclusions

Observations to date on macroscopic examination inflation-fixed lungs with use of ordinary dissect- croscopes, supplemented by ultrasoft radiogra- y lead to three main conclusions.

First, the common form of chronic emphysema ms to develop first in small localized areas which e a high correlation with trapped parenchymal t deposits. In the areas of early emphysema, two nomena appear to be more basic than the air dilatation itself. One is abnormal fenestration in eolar septums; the other is increased diameter lveolar ducts, seemingly due to "relaxation" of r spiral musculature. I believe that these two ie defects tend to destroy the geodesic pattern ension balance in the lung which in turn impairs perfect equalization of inflow and outflow of

. 8.—Photograph looking into alveolar duct. From 1- thick slice of wet-inflation fixed lung (with use of 's solution) through main bronchus. Pressure of 25 cm. ter was maintained constantly for three weeks in order ung would be thoroughly fixed in inflated state. Knob- tructures passing over this particular spiral ridge of lar duct are precapillary size blood vessels (× 120).

Emphysema would, therefore, appear to be resultant of tissue defects and disarrayed me- ical forces. Second, the lung has a semi-shunt ular structure in the periphery of lobes which lieved to be related to rapid changes in blood-flow requirements. Third, small pulmonary vessels are found protruding into the lumina of alveolar ducts. This is most conspicuous at points where the vessels pass over certain ridges of spiral musculature of the alveolar ducts. This tends to support the suggestion reported by Riley[10] that small pulmonary vessels at some point traverse a boundary from the low-pressure area existing outside the air passages to a higher pressure area such as normally exists inside the air passages.

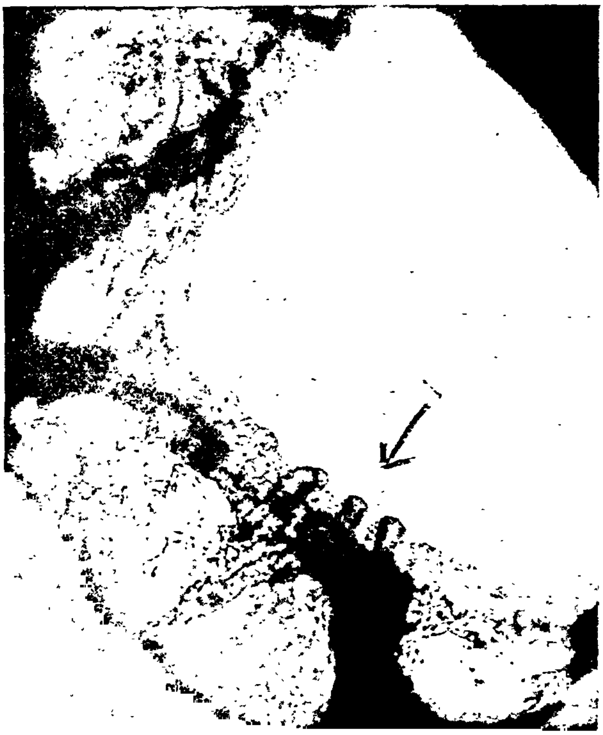

Fig. 9.—Photograph looking into lumen of alveolar duct. From 1-mm.-thick slice of lung, vessels of which were injected with colored latex at 180 mm. Hg pressure. After hardening of latex, lung was sliced and preserved in formalin. Precapillary vessels are seen hooking over spiral muscle (× 134).

Microradiographs of alveolar ducts showing the spiral musculature will be found in the Proceedings of Second International Symposium on X-ray Microscopy, New York, Academic Press, Inc., to be published.

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The technical work for this study was done by Messrs. Michael Dauzat and Edward Momtamat.

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effort, the exit tubes from the diseased area actually close or not depends on an interplay between the forces in the diseased parenchyma on the one hand, and forces in the surrounding normal lung and chest walls (including diaphragmatic "wall") on the other. Expiratory "obstruction" (probably at respiratory bronchiole level), according to my view, could be said to come about as a result of localized diseased parenchyma combined with expiratory effort beyond a given threshold of forcefulness. Augumented resistance in either or both phases of respiration tends to reduce the amplitude of the pressure changes between full inspiration and full expiration.

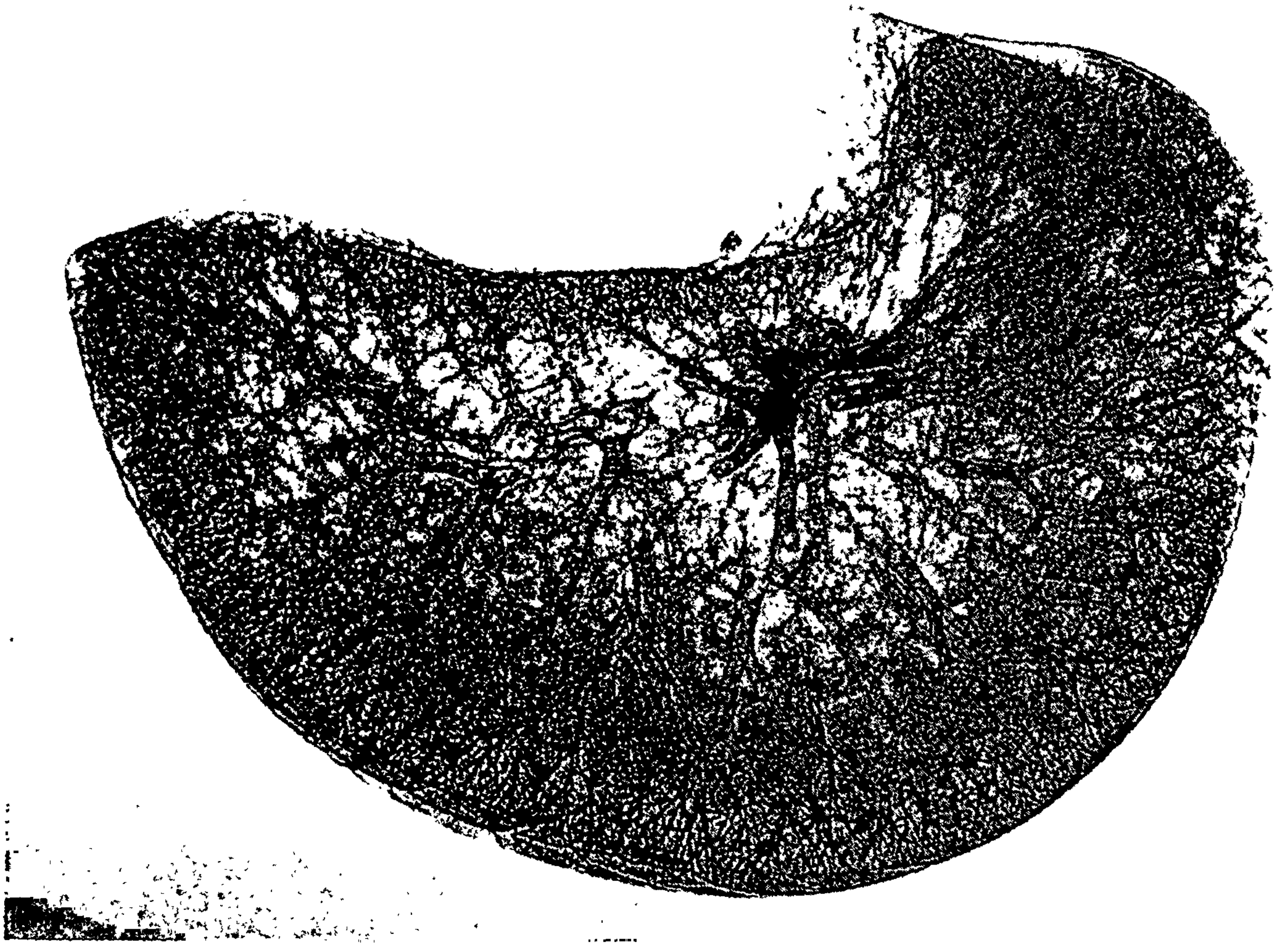

Fig. 7.—Radiograph of entire cross section of dry-inflation fixed lung cut 4 mm. thick, showing peripheral zone in which small vessel network is much denser than elsewhere.

This leads to less thoracic pumping action on both air and blood as they pass through their respective trunks, which are interstitially located.

I do not have any further morphologic findings that bear on the pumping action produced on air; but in the case of blood, the finding of precapillary size vessels projecting into alveolar ducts was of considerable interest. As pointed out by Riley,[10] in reporting the work of Howell, Permutt and Proctor, the pulmonary vascular system seems to be divided into two compartments, one consisting of the arteries and veins and the other mainly of capillaries. These workers found that the volume of blood in the "artery-vein" compartment increases with inspiration, while the volume of blood in the "capillary" compartment decreases. The implication of this finding is that, at some point, the blood vessels pass from the outside of air passages, where low pressure (more negative than intrapleural pressure) exists, to the inside of the air passages where a relatively high but nevertheless variable pressure exists. Under certain localized pathological conditions abnormally high or low pressures might be maintained continuously, in which case blood would automatically be shunted away from or toward the involved area. The lumina of the "inside" vesse might also be altered by changes in the chemist of the local gas mixture or by changes in the ton of the local spiral musculature.

The peripheral semi-shunt vascular zone, whic was visualized with relatively thick dry lung slices is believed to be partially closed during rest. B opening up at the times of physiological emergency it could temporarily sustain a fast return of bloo to the heart, possibly at the price of some degre of incomplete oxygenation. What constitutes a "physiological emergency" depends partly on work

Partial oculomotor palsies are noted because the patient complains of diplopia. Recognizable diplopia, as interpreted by the patient, is due to a divergence of the visual axes. Such divergence may be measured in prism diopters, either vertically or horizontally, provided there is reasonably good vision in each eye.

For those who wish mathematical confirmation of opinions, let us again note that ordinary neurological examination of the nerves under consideration will show paralysis measurable at 90 prism diopters. This paper illustrates ophthalmological diagnosis of diplopia of 4-to-6 prism diopters. By means of the methods described, one can find, therefore, a cranial nerve palsy 90% earlier than by other methods.

Clinicopathological Relationship.—Classification of partial oculomotor palsies as early cerebrovascular stroke, under the definition "a local neurologic disorder of abrupt development due to a pathologic process in a blood vessel," [2] is generally accepted.

Dreyfus and co-authors [3] described how difficult it was to find the vessel to a given cranial nerve, but believed, along with many others,[4] that the cause of such nerve lesions is generally vascular. Hyland and Barnett [5] gave ample pathological proof of early and recurrent hemorrhage into oculomotor cranial nerves.

Whether we classify [2] the pathological lesion as infarction, ischemia, or hemorrhage, or whether we classify this syndrome as "of undetermined origin," [6] the methods described allow us to measure reliably the onset and clinical course of the condition and often the recovery of the involved cranial nerve. The clinical diagnosis, though made by inference, is supported by a laboratory (prismatic measurement) finding of sudden diplopia, more often a vertical diplopia, frequently of between 4 and 10 prism diopters.

This finding should be given equal diagnostic weight with other types of laboratory findings, such as bloody spinal fluid, abnormal arteriogram, or hemianopsia.

Once evidence of vascular leakage into a cranial nerve has been detected, one may try to refine the diagnosis by determining the type of vascular disease present, such as aneurysm, sclerosis, hypertension, polycythemia, stress, trauma, angioma, diabetes, cardiac disease, or embolism. Management of the vascular leakage is primarily medical, with occasional observation of the diplopia. Primary treatment of the diplopia with prisms may lead to neglect of the medical aspect. With regard to this syndrome, one must emphasize the diagnostic value of prisms and deemphasize their therapeutic use.

Pathology

The basic pathological process in this syndrome, as in other cerebral vascular disease,[2] consists of three separate aspects, as follows: 1. The vessel is occluded, or ruptured, because of vascular disease. 2. The cerebral tissues suffer either infarct or hemorrhage. 3. A focal neurological disorder results. In early lesions of this type, the infarct or hemorrhage is usually only a few millimeters in size and often contained within the nerve sheath. Little is gained from illustrating large gross lesions at autopsy. Hyland and Barnett [5] illustrated both old and recent intraneural hemorrhage so well that reference should be made to their illustrations.

Pathological proof of the small lesion that is being considered is neither possible [7] nor desirable at the early stage of the disease, provided there is positive evidence of (1) vascular disease, (2) focal neurological deficit in the oculomotor nerves, accurately measurable by prisms, (3) sudden onset, and (4) due consideration of the differential diagnostic possibilities.

Since the clinician's interest is in the living patient and he cannot hope to differentiate between small infarcts and hemorrhages, nor always between the various types of vascular pathology in the vessels, I accede to use of the term "cerebrovascular insufficiency." While this terminology has been applied to other types of cerebrovascular disease,[8] it has not been used with regard to ophthalmic syndromes.

I therefore offer, for the convenience more of ophthalmologists than of neurologists, a classification of the eye findings to be noted in various stages of cerebral vascular insufficiency.

Cerebral Vascular Insufficiency: Ophthalmic Syndromes.—It is not difficult for the ophthalmologist to make an early clinical diagnosis of weakness in the cerebral vascular system. Three stages of vascular disease of the brain may readily be noted (see the table).

Progressive vascular damage, as noted by the symptoms in the three stages of cerebral vascular insufficiency, lead to progressively severe organic damage to the brain.

In stage 1, a small vessel has sprung a leak or become obstructed, whereas in the subsequent stages the extravasation or infarct has resulted in a progressively larger brain hemorrhage or destruction.

Results of lumbar puncture in the three stages frequently are as follows: stage 1, low spinal fluid pressure, elevated protein level (with return to normal); stage 2, higher pressure, early appearance of red blood cells in the fluid, later xanthochromia of cerebrospinal fluid (with return to normal in many cases); and stage 3, large intracranial hemorrhage. Lumbar puncture often is precluded, unless a neurosurgeon is in attendance to operate in case of herniation of the brain stem.

Arteriography should not be performed to satisfy medical curiosity.[11] Many patients with diseased cerebral vessels will survive longer on medical therapy than with too early intervention. Arteriog-

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OPHTHALMIC DIAGNOSIS AND MANAGEMENT OF IMPENDING CEREBROVASCULAR LESIONS

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Diplopia is one of the earliest signs of cerebral vascular insufficiency. It may be a complete oculomotor palsy when the lesion is large and late, or it may be so slight that the patient is not aware of it except as an ocular discomfort or refractive disorder. Using the tools of the ophthalmologist—lenses; prisms; and tests of fusion, depth perception, and accommodative power—the examiner can often find these signs of oculomotor weakness long before other neurological findings are apparent. The author classifies the diagnosis of cerebral vascular insufficiency, including such ocular signs and symptoms, gives illustrative patient histories, and brings attention to the management of eye difficulties in patients with strokes.

The purpose of this report is to illustrate that ophthalmic findings of sharply defined early cerebrovascular disease are often overlooked and not generally appreciated by the medical profession at large.

Reliable criteria for clinical ophthalmological diagnosis of early cerebrovascular disease will be discussed. When applied more widely, they will lead to early diagnosis and greater longevity and result in fewer complications than angiography and air study in the management of patients with stroke in its early stage.

Clarity of thinking and mutual understanding of the tools used by cooperating specialists will lead to better diagnosis and management of cerebral vascular disease.

Ophthalmology, the oldest specialty, is renowned for its use of the ophthalmoscope as a diagnostic instrument. In this contribution, however, I will discuss the use of prisms as a primary diagnostic tool, assigning to the ophthalmoscope and the visual field[1] examination secondary roles. A prism test is of the nature of a laboratory test, and the ophthalmic examiner, of a technician.

Methods

Of the several ophthalmic syndromes which clinically suggest cerebral vascular disease or stroke,[1] this contribution refers primarily to one, namely, the syndrome of paralysis of the extraocular muscles of rotation of the globes. These muscles are supplied by the 3rd, 4th, and 5th cranial (oculomotor, trochlear, and trigeminal) nerves, which have centers for coordinating action in the brain stem. Ordinary neurological diagnosis of these palsies is limited to gross observation. Gross observation can detect an extensive paralysis which often measures a maximum of 90 prism diopters. Partial palsies are diagnosed grossly on the basis of the medical history and are more often than not confused with refractive complaints, ocular neuroses, hysteria, and long-standing ocular muscle abnormalities, which in ophthalmic terms are called "phoria."

Associate Ophthalmologist, Hartford Hospital, and Assistant Clinical Professor of Ophthalmology, Yale University, New Haven.

An 18-month follow-up of her progress since recovery disclosed no further vascular complication.

CASE 2.—An executive was referred to me by a plant physician because he had had blurred vision for four days prior to the visit. He was a 58-year-old man who had noted dilatation of his left pupil on Aug. 6 and was examined in my office on Aug. 7, 1958. He stated that he had had attacks of blurring vision four or five times for short periods in the preceding five years.

Examination on Aug. 7, 1958, suggested that a mild degree of diplopia was present, but results of the tests were not specific and definite. He had 20/20 vision and good depth perception. His hyperphoria of 1 D. susided to zero later in the day. His retinal arteries showed minor narrowing, and his retinal veins were slightly dilated. The plant physician had placed him on therapy with small doses of reserpine (Serpasil), because his blood pressure had been elevated. Since a marked change in his vision was noted, his glasses were changed, and he was given a follow-up appointment for three weeks ater.

Before a week had elapsed, the patient requested nother examination and complained of many seri-us ocular problems. He had had an accident while driving, and he had diplopia much of the time, which he could overcome only by closing one eye. Stairways appeared tipped to him, and he could not shave unless he closed one eye. He believed hese disturbances were due to his new glasses.

Examination at this time revealed a 5-D. hyperphoria, and his depth perception was severely mpaired. The diplopia field showed that the left uperior rectus muscle was weakened, but the upils were equal at this time.

The diagnosis was cerebral hemorrhage into the eft third cranial (oculomotor) nerve. Prisms were ot prescribed for his glasses at this time, because seemed desirable to await maximum improvement. The patient was instructed to attempt to keep is vision single by using the right lower quadrant f his field of vision, and three months' rest was ecommended. He was kept under observation.

The patient was unable to stand more than six eeks of rest, however, and thereafter returned to alf-days at work. He soon felt it necessary to un-ertake a few business trips, and prisms were laced in his glasses.

In the 16-month follow-up of the patient's prog-ess since recovery, there have been no further cular complaints or vascular complications. The atient requires lenses with 2 prism diopters verti-ally, for comfort in binocular vision. He has re-umed his full work load and drives his car with ase. He still has 20/20 vision in each eye. He is aking reserpine (Serpasil) under the direction of is physician.

CASE 3.—A 70-year-old male patient stated that e had had trouble, of one month's duration, in ocusing his eyes when he looked to the right. His vision was not clear, and he thought he almost saw double. He had no headache or ocular discomfort. The glasses which he used for reading contained no prism and were four years old.

Examination revealed a 3-prism diopter left-sided hyperphoria for distant vision and exophoria of 14 prism diopters for near vision. The remaining findings of the examination were normal but for a grade 2+ sclerosis of the choroidal vessels in the retina. His vision, with correction, was 20/20 and 14/14 respectively.

This patient first noted ocular symptoms when reading. It is interesting to note that he had recently retired and was unhappy in retirement. He had been looking for another position. It is possible that the nervousness generated by not working led to this case of probable vascular disease. He also showed a rather severe dermatitis of his hands which, according to his physician, was due to nervous tension and also believed to be due to his nervousness over not working.

This is a case in which the vascular accident occurred because of the patient's retirement and in which retirement probably should not be advised as therapy. The patient was given sedatives and 2-prism diopters, base down, in the lens for the left eye were prescribed for both distant and near vision. He was told to return in three to six months to ascertain if the prism could be removed, but he has not returned at the time of writing.

CASE 4.—A 48-year-old machinist had been periodically examined for glasses since 1950. In August, 1957, he first noted double vision while he was on his vacation. When asked if it could have been present longer, he said that he had had trouble parking his car during the month prior to this consultation, together with other evidence of disruption of depth perception.

The family history included diabetes in a brother and a sister, and the patient had had moderately controlled diabetes for seven or eight years. His last blood sugar determination, prior to 1957, was 165 mg.%. He rarely had any sugar in the urine. He had been reducing his weight from 220 to 195 lb. (99.8 to 88.5 kg.).

Examination revealed a 25-prism diopter esophoria for distance (19-prism diopters for near vision, with a 1-prism diopter right-sided hyperphoria). His retinal arteries also appeared nearly normal, although there was a grade 1 narrowing. The diagnosis was vascular insufficiency due to diabetic vascular disease. The patient was hospitalized to control his diabetes and to assist in the absorption of the hemorrhage around the left 6th cranial (abducens) nerve. He recovered and has been symptom-free for three years.

CASE 5.—A 61-year-old woman had had diabetes since 1933 and first consulted me in 1956 because she awoke with "cobwebs" before her right eye. Examination revealed diabetic retinopathy and in-raphy, or the stress involved, may rapidly push a patient with stage 1 vascular insufficiency into stage 3. It is not disputed that in stage 1 the vascular tree is better able to stand arteriography without resulting complications than it is in the state of advanced disease of stage 3.[11] It is a matter of delicate judgment whether to try to maintain a patient with stage 1 disease for years on office treatment or to risk complications by subjecting him to further study. It must be noted that surgical clipping of one aneurysm does not preclude the formation of others in a weakened vascular tree.

Diagnosis of Cerebral Vascular Insufficiency by Symptoms and Findings

- Stage 1, early: office diagnosis
  - Symptoms and findings (some or all)
    - Evidence of aging
    - Fatigue, often undue stress
    - Nervous symptoms, insomnia
    - Ophthalmic findings
      - Retinal vascular changes
      - Retinal hemorrhages (38% with aneurysms)[9]
      - Diplopia: recent origin, usually "vertical," due to partial oculomotor palsies
      - Optic atrophy, occasionally
      - One-sided reduction in retinal artery pressure of 15-25 mm. Hg, as measured with ophthalmodynamometer or other means [10]
    - Headache
    - Noises in head (bruit)
- Stage 2, moderate: hospital cases
  - Symptoms and findings (some or all)
    - As in stage 1, with addition of:
      - Severe headache
      - More retinal vascular changes and hemorrhages
      - Papilledema (50% in aneurysms)
      - Definite oculomotor palsies, often complete
      - Subarachnoid hemorrhage (82% or more with aneurysms)
      - Hemiparesis, hemiplegia, or hemianopsia, transient or permanent
      - Pupillary changes
      - Blindness
- Stage 3, advanced, acute: hospital cases
  - Symptoms and findings (some or all)
    - As in stages 1 and 2, with addition of:
      - Critical illness of patient
      - Coma, disorientation, or aphasia
      - Brain stem signs: nystagmus, internuclear ophthalmoplegia
      - Bilateral or homonymous hemianopsia, hemiplegia, etc.
      - Decerebrate rigidity, convulsions
      - Death

Importance of Location of Vascular Lesion.—The location of the vascular lesion which brings about the diagnosis is one of pure chance. The most frequent locations of hemorrhages and aneurysms are where the greatest mechanical stress is placed on a cerebral vessel,[12] namely, in the carotid, anterior, or middle cerebral arteries. Sclerosis, and often arteritis, occur quite generally, and emboli or infarcts occur secondarily to other vascular disease in all parts of the brain.

The location of the lesion is of primary importance in the prognosis, for in many areas any clinically recognizable lesion is fatal. The location of the lesion also determines the symptoms and thus frequently the specialist to whom the patient turns for diagnosis and treatment.

Clinical Diagnosis

The committee for the National Institute of Neurological Diseases states:[2] "the finding of . . . ocular or gaze paralysis . . . provides unequivocal evidence of the focal character of the brain disease. . . ." They emphasize the importance of a clear history of the mode of onset, evaluation, and course of each symptom taken in relationship to the medical status at that time—which is of the utmost importance.

It is generally agreed that a minority of intracranial hemorrhages do not produce bloody spinal fluid.[13] The syndrome under discussion belongs to this minority; it does not usually cause bloody spinal fluid. It is usually associated with moderate chronic headache of recent onset. It usually is not associated with stiff neck, coma, or cranial bruit (except after several attacks). It is often associated with hypertension, arteriosclerosis, or diabetes, and obesity, together with stress.

Angiography and ventriculography, and even lumbar puncture, subject the patient who is in the early stage of cerebral vascular insufficiency to pain and possible complications and often prolonged convalescence. These diagnostic tests should be reserved for the moderately ill patient.

Illustration of Ocular Clinical Diagnosis by Case Histories

CASE 1.—A well-preserved and vivacious woman aged 76 years was referred to me four weeks after she had been hospitalized with a "stroke," in which her left side had been paralyzed. She remained in the hospital two weeks, recovering the use of her left arm and leg.

Two weeks after returning home, she developed a sudden complete paralysis of her right 3rd cranial (oculomotor) nerve, with pain, ptosis, dilated pupil, and her eye in the down-and-out position. She walked into my office; I reported to her physician that she had an extensive vascular lesion, probably an extension of the one which had occurred four weeks previously. In addition to involvement of the right third cranial nerve, there was a homonymous hemianopsia on the left. No paralyses in arms or legs were present.

After three months of regulated rest and therapy she returned to my office, her condition remarkably improved. Her vision was 20/20 in each eye. The homonymous hemianopsia had receded to a quadrantal area, and the lesion of the 3rd cranial nerve had improved sufficiently so that gross recognition of it was impossible. She had no diplopia.

Her physical appearance was excellent, but her level of nervous tension was considered too high. She spoke in rapid-fire sentences. She refused sedation but was agreeable to taking small doses of reserpine (Serpasil).

In recent years the clinical diagnosis of cerebral aneurysms has been facilitated by the teachings of Cushing, Adson, Dandy, and other neurosurgeons, and the ophthalmologist, who should make a great percentage of the initial diagnoses, may contribute much to the ease of diagnosis by frequently noting early and partial oculomotor palsies, during his office examinations.

Jefferson[16] expressed the opinion commonly held today that "the commonest cause of isolated oculomotor palsy is the supraclinoid carotid aneurysm."

Hyland and Barnett[5] correlated the clinical evidence of cranial nerve involvement with autopsy findings and described 21 aneurysms in which one of the oculomotor nerves was either adherent to, or actually incorporated in, the wall of the aneurysmal sac. They described 19 other cases of aneurysmal bleeding which secondarily affected oculomotor nerves, by either pressure or kinking. In 10 of their cases they found evidence of old hemorrhage withn the substance of a cranial nerve, supporting the contention that intermittent, recurrent leaks occur, t intervals of several months or several years.

It is the first leak that should be noted by the phthalmological examiner. He does not need to wait for diplopia of 70-to-90 prism diopters when he an easily diagnose a diplopia of less than 10-prism iopters.

Jefferson,[16] in describing his personal observaons in 158 cases of oculomotor palsy due to neurysms, found that 70% showed evidence of akage from the aneurysm, while only about 10% ad severe or fatal subarachnoid hemorrhage, inially. The syndrome, as described by Jefferson, sually led to ligation of the carotid artery or the neurysm, while my interest is in an earlier stage, hich may be treated medically.

The syndrome described by Jefferson is a rather lvanced form of the disease. The sufferers noted sudden onset of ptosis and mydriasis after a few ays of diplopia. Pain so severe as to require administration of analgesics and hospitalization was cated in the forehead, ipsilateral, in the eye, and own the side of the nose. Persistent pain was the ost informative sign of activity of the aneurysm nd the primary indication for surgical intervention. Of great importance is Jefferson's comment that any patients did well without operation. That is ue today, especially when diagnosis is made early.

Differential Diagnosis and Prognosis

Cerebral vascular lesions may be accurately diagosed at autopsy. To be of more than technical or atistical interest, however, diagnosis must be made inically and in stage 1 of vascular insufficiency ther than when vascular disintegration has set in—e stage of prolonging life, rather than the stage prolonging death.

Aside from congenital and traumatic aneurysms, ere is a large group of aneurysms which develop later life. Whether these develop from congenitally weakened areas in the vessel walls, in a manner similar to the development of an inguinal hernia in middle age, or whether they develop on the basis of arteriosclerosis and hypertension can only be conjectured. There are also the diabetic types of aneurysm in the retina that are so familiar to the ophthalmologist. However aneurysms develop, they eventually leak and often rupture.

Spontaneous rupture of a cerebral vessel may usually be attributed to (1) aneurysm, (2) infarct or embolus, (3) thrombosis, or (4) arteritis.

In retrospect, the term "spontaneous" usually means that early diagnosis of vascular insufficiency was not made. If the ophthalmologist will consider the possibility of lesions of the vascular tree as he does that of glaucoma, every time he prescribes glasses, earlier diagnosis will be possible.

Differentiation between vascular lesions and brain tumors or infections, including bulbar poliomyelitis, usually is readily made when all factors are considered.

Disseminated sclerosis and myasthenia gravis often cause ocular muscle palsies, but neither suddenly nor often in association with pain, and usually in combination with other diagnostic criteria. Periodic ophthalmoplegic migraine has been designated as a cause of oculomotor palsies. The obscurity of its cause may be cleared up in time, and it would not be surprising if the condition were frequently due to leakage from a vascular defect.

Arteritis, including temporal arteritis, periarteritis nodosa, pulseless disease, and other forms of inflammatory arterial disease are diagnosed by laboratory evidence of inflammation, such as increases in the blood sedimentation rate, eosinophilia, and other findings suggestive of these conditions. Rarely does arteritis resemble "spontaneous intracranial hemorrhage."

Emphasis must be placed on the early diagnosis of oculomotor signs, which in most cases are more frequent and appear earlier than visual field defects or loss of visual acuity; they are also recurrent.

The seriousness of the diagnosis of cerebral vascular insufficiency is so great that caution must be emphasized in making such a diagnosis on the basis of ophthalmic findings.

Medical or surgical treatment requires a radical change in work and living habits and usually entails an economic loss to the patient and his family. Errors are costly, when made either too early or too late.

Final diagnosis in all cases is determined by the autopsy report, and often the ophthalmologist will turn over the making of the clinical diagnosis to the neurosurgeon, with performance of arteriography, ventriculography, and lumbar puncture. This often leads to surgical exposure, with a resultant average survival rate for patients with all types of surgical cerebral vascular lesions of about 58% (Henderson).

creasing haze in her right vitreous body which was diagnosed as inflammation of the vitreous body due to the large number of cells present.

In view of the frequency with which this type of inflammation fills the vitreous body with dense fibrosis, the patient was placed on prednisone (Meticorten) therapy under the care of her diabetic specialist. After six weeks' treatment her vision definitely improved, but administration of the prednisone had to be stopped because she developed cystitis.

Shortly thereafter, her gallbladder troubled her and was removed surgically. In December, 1956, she came to me for a follow-up eye examination. It was noted that the vitreous clumps had receded, but that there had been an increase in the diabetic retinopathy, especially in the right eye. She complained of a noise in the right side of her head and of nervous symptoms. A neurosurgical consultation was obtained, and it was reported that the noise could be heard by stethoscope and even with the examiner's ear against the patient's ear. Her blood pressure was 210/110 mm. Hg when she became excited. She was described as an extremely anxious and labile personality. Lumbar puncture was performed in the hospital and showed an elevation of protein content to a level of 106 mg.%. Electrocardiographic findings were normal. It was decided that it would be better to leave her aneurysm untied, since there was also a question of an innominate fusiform dilatation. The neurosurgeons stated that, if the aneurysmal noise increased, they would perform an angiogram. Findings of a roentgenogram of the skull were normal. This patient was maintained on medical and diabetic therapy for six months. In August, 1957, she developed complete paralysis of the left lateral rectus muscle; a diagnosis of cerebrovascular insufficiency with leakage was made. The patient was treated at home. She has recovered vision in each eye but still has an annoying bruit at times of excitement.

Case 6.—A 61-year-old man in April, 1957, noted double vision of such a degree that he had to cover his right eye. He had had a vascular episode in 1948 which had cleared up in four weeks. This episode of 1948 occurred in the retina and left visible scars and some new vessel formation.

His business problems had been increasing constantly; he was under duress at the time the double vision developed in 1957, and since he found it impossible to cut his work load in any way, he was advised to retire.

The double vision caused sudden development of a 9-prism diopter hyperphoria in the right eye and a 7-prism diopter exophoria and was diagnosed as a partial palsy of the 3rd cranial (oculomotor) nerve. His blood pressure was 200 mm. Hg systolic, and his retinal arteries were narrowed to grade 2 or 3, with extensive sclerosis. He was hospitalized for medical and neurological consideration, but it was not considered safe to perform an angiogram on him. His headaches decreased after one week in the hospital, and his condition slowly improved after he had reorganized his life. Two years later, at the time of writing, the patient is well and happy.

Case 7.—A 57-year-old man had been given occasional ophthalmological examinations for 11 years, with entirely normal findings until 1951, when he suddenly developed double vision. This occurred as he was leaving his house and getting into his automobile. When he reached his office, he found it difficult to get downstairs. Everything he looked at seemed out of focus, and he had trouble reading his mail. His speech and orientation were normal on examination. His knee jerks were good. He had mild sclerosis of the retinal arterioles, and eye examination revealed a 2-prism diopter hyperphoria in the left eye which had never shown before. All other findings of the eye examination were normal. Results of his blood tests were negative. His blood volume, however, showed an 860-cc. excess of total blood volume, a 462-cc. excess of plasma volume, and a 336-cc. excess of red blood cell volume. His retinal veins showed grade 2 dilatation.

The patient was referred to his physician with the diagnosis of small intracranial vascular damage (insufficiency) and was placed on general treatment. He returned to work in about three weeks without further difficulty.

This patient has lived a moderately quiet life for six years, at the time of writing, and has had no recurrence of cerebral signs, although he suffered one coronary attack within the past year. In August, 1958, he was hospitalized with venous thrombosis in the legs and thus far has made another recovery. Polycythemia and stress apparently reactivated his various vascular episodes.

Comment

Cerebral vascular "accidents" account for the greatest morbidity and mortality in patients with all types of vascular lesions who pass through the hands of the ophthalmologist.

Even more important than coronary vascular disease, in which the ophthalmologist may only play a secondary role as prognostician, are the cerebral vascular diseases which offer the ophthalmologist a role encompassing diagnosis, therapy, and management. The possibility of confusion between cardiac and cerebral syndromes[14] should be noted, however.

That cerebral aneurysms may cause oculomotor palsies has long been surmised,[15] but the clinical picture was not established until 1923 (C. P. Symonds). The diagnosis has always been considered difficult, even though many large series of aneurysms have repeatedly shown the high incidence of oculomotor nerve involvement. (*Fearnsides*, 1916, 44 in 5,532 autopsies; Osler, 1921, 12 in 800 autopsies; and McDonald and Karle, 1939, in 1,125 reported cases.)

In recent years the clinical diagnosis of cerebral aneurysms has been facilitated by the teachings of Cushing, Adson, Dandy, and other neurosurgeons, and the ophthalmologist, who should make a great percentage of the initial diagnoses, may contribute much to the ease of diagnosis by frequently noting early and partial oculomotor palsies, during his office examinations.

Jefferson[16] expressed the opinion commonly held today that "the commonest cause of isolated oculomotor palsy is the supraclinoid carotid aneurysm."

Hyland and Barnett[5] correlated the clinical evidence of cranial nerve involvement with autopsy findings and described 21 aneurysms in which one of the oculomotor nerves was either adherent to, or actually incorporated in, the wall of the aneurysmal sac. They described 19 other cases of aneurysmal bleeding which secondarily affected oculomotor nerves, by either pressure or kinking. In 10 of their cases they found evidence of old hemorrhage within the substance of a cranial nerve, supporting the contention that intermittent, recurrent leaks occur, at intervals of several months or several years.

It is the first leak that should be noted by the ophthalmological examiner. He does not need to wait for diplopia of 70-to-90 prism diopters when he can easily diagnose a diplopia of less than 10-prism diopters.

Jefferson,[16] in describing his personal observations in 158 cases of oculomotor palsy due to aneurysms, found that 70% showed evidence of leakage from the aneurysm, while only about 10% had severe or fatal subarachnoid hemorrhage, initially. The syndrome, as described by Jefferson, usually led to ligation of the carotid artery or the aneurysm, while my interest is in an earlier stage, which may be treated medically.

The syndrome described by Jefferson is a rather advanced form of the disease. The sufferers noted a sudden onset of ptosis and mydriasis after a few days of diplopia. Pain so severe as to require administration of analgesics and hospitalization was located in the forehead, ipsilateral, in the eye, and down the side of the nose. Persistent pain was the most informative sign of activity of the aneurysm and the primary indication for surgical intervention.

Of great importance is Jefferson's comment that many patients did well without operation. That is true today, especially when diagnosis is made early.

Differential Diagnosis and Prognosis

Cerebral vascular lesions may be accurately diagnosed at autopsy. To be of more than technical or statistical interest, however, diagnosis must be made clinically and in stage 1 of vascular insufficiency rather than when vascular disintegration has set in—the stage of prolonging life, rather than the stage of prolonging death.

Aside from congenital and traumatic aneurysms, there is a large group of aneurysms which develop in later life. Whether these develop from congenitally weakened areas in the vessel walls, in a manner similar to the development of an inguinal hernia in middle age, or whether they develop on the basis of arteriosclerosis and hypertension can only be conjectured. There are also the diabetic types of aneurysm in the retina that are so familiar to the ophthalmologist. However aneurysms develop, they eventually leak and often rupture.

Spontaneous rupture of a cerebral vessel may usually be attributed to (1) aneurysm, (2) infarct or embolus, (3) thrombosis, or (4) arteritis.

In retrospect, the term "spontaneous" usually means that early diagnosis of vascular insufficiency was not made. If the ophthalmologist will consider the possibility of lesions of the vascular tree as he does that of glaucoma, every time he prescribes glasses, earlier diagnosis will be possible.

Differentiation between vascular lesions and brain tumors or infections, including bulbar poliomyelitis, usually is readily made when all factors are considered.

Disseminated sclerosis and myasthenia gravis often cause ocular muscle palsies, but neither suddenly nor often in association with pain, and usually in combination with other diagnostic criteria. Periodic ophthalmoplegic migraine has been designated as a cause of oculomotor palsies. The obscurity of its cause may be cleared up in time, and it would not be surprising if the condition were frequently due to leakage from a vascular defect.

Arteritis, including temporal arteritis, periarteritis nodosa, pulseless disease, and other forms of inflammatory arterial disease are diagnosed by laboratory evidence of inflammation, such as increases in the blood sedimentation rate, eosinophilia, and other findings suggestive of these conditions. Rarely does arteritis resemble "spontaneous intracranial hemorrhage."

Emphasis must be placed on the early diagnosis of oculomotor signs, which in most cases are more frequent and appear earlier than visual field defects or loss of visual acuity; they are also recurrent.

The seriousness of the diagnosis of cerebral vascular insufficiency is so great that caution must be emphasized in making such a diagnosis on the basis of ophthalmic findings.

Medical or surgical treatment requires a radical change in work and living habits and usually entails an economic loss to the patient and his family. Errors are costly, when made either too early or *too late.*

Final diagnosis in all cases is determined by the autopsy report, and often the ophthalmologist will turn over the making of the clinical diagnosis to the neurosurgeon, with performance of arteriography, ventriculography, and lumbar puncture. This often leads to surgical exposure, with a resultant average survival rate for patients with all types of surgical cerebral vascular lesions of about 58% (Henderson).

Oculomotor Findings in Cerebral Vascular Insufficiencies

Diplopia is one of the earliest signs of cerebral vascular insufficiency. It may be a complete oculomotor palsy when the lesion is large and late or it may be so small that the patient is not aware of it except as an ocular discomfort or refractive disorder.

In using the tools of the ophthalmologist—lenses; prisms; and tests of fusion, depth perception, and accommodative power—the examiner can often find these signs of oculomotor weakness long before other neurological findings are apparent. There are at least three factors that make these important refractive tests of muscle function of less potential than actual value, especially in early cases of the condition in which they should be of greatest value.

The first failure of these tests is due to the examiner's voluntarily omitting them. He may be rushed; the patient may give a history of only slight reading difficulty; and the examiner may assume that all he needs to do is strengthen the reading addition in the patient's glasses. Without performance of the tests the diagnosis can hardly be made.

Another failure of these tests of oculomotor function occurs when the patient is slightly confused, as he may be after a mild spell of cerebral vascular insufficiency. Mental confusion and fatigue and nervous symptoms frequently are associated in cerebral vascular lesions. It is important for the examiner to use a technique that allows him to ascertain small degrees of oculomotor weakness under difficult examining conditions. Herein lies the importance of a medical examination, rather than one by a technician without medical knowledge and judgment. This point is sometimes difficult to emphasize.

Ocular muscle abnormalities are common findings during tests of refraction. They may be of long standing, or even congenital, and evidence of cerebral vascular damage may be superimposed on long-standing ocular muscular abnormality, so that the examiner must have methods of determining which are the old and which the recent muscle changes.

Tests for Oculomotor Weakness

Cover Test.—In the cover test the eyes are focused on one point, while the eyes are alternately covered, and the jump of each eye to the point of fixation is gauged. This is done in the various positions which each of the 12 oculomotor muscles control and, in large recent muscle weaknesses, shows the most positive findings. The weaker muscle moves more slowly and is thus diagnosed.

Examination of Each Ocular Image, with Relation to Its Fellow.—This test is performed by means of two different colored glasses to differentiate the two images, while the eyes focus on one light source. This test may be refined so that small degrees of abnormality may be diagnosed positively. It is often done with a Maddox rod, which refines the light seen to a small linear image and makes possible diagnoses of 0.5-prism diopter changes.

Prismatic Measurement, by Means of Loose Prisms.—If loose prisms, varying in power from 0.5 to 50 D. are used, the power required to move the image of one eye back toward its normal position can be read off and the weakness of the particular ocular muscle determined.

A complete ocular muscle palsy may be grossly noted by any examiner. It usually will measure over 60 D. of prism power, in the position of greates deviation, and will decrease toward the position o least power of the affected muscle. In other words *it will increase in the sphere of action of the* affected muscle.

The type of ocular muscle weakness being emphasized in this study is one beginning at prism diopters and usually not exceeding 10 or 1 prism diopters in its greatest extent. When such deviations are found, especially in the vertical components, they usually indicate, after sudden onset a partial oculomotor palsy.

The patients in the cases I have described hav been observed to undergo either complete or partial retrogression in less than one year, and convalescence may be estimated by improvement i the measurement of the deviation. Many of m patients received a diagnosis and were treated successfully in stage 1, with resultant survival of ove 10 years.

Management of Early Cerebral Vascular Insufficiency

Composite Case.—A composite case of early (stage 1) cerebral vascular insufficiency, in which the diagnosis could be made by an ophthalmologis in his office, would include many of the following findings:

History: The patient would be a male executive aged 57 years, under medical treatment for hypertension, possibly with mild diabetes and overweight He would report severe headaches, of recent origin and some difficulty when driving and reading, also of recent onset. He may have had one mild coronary attack. There would be no fever or history of severe illness of acute nature.

Examination: Ophthalmic findings would show vision corrigible to 20/20 with glasses, and often the lens(es) the patient was using would be satisfactory without change, in spite of his complaints Visual field findings would be normal. Ophthalmoscopy would show hypertensive retinal arteriolar changes of grade 2 or 3. The external eye and pupillary findings would be normal.

tion should a short circuit develop, as he is with equipment operated by alternating current, nor is he at the mercy of a power line failure or an accidentally pulled power cord.

Several recent developments in electronics make this practical and reliable pacemaker possible; namely, the transistor, improved mercury cell batteries, and miniature components, together with advances in plastics and insulating materials. The transistor offers several advantages over the vacuum tube in pacemaker application. These advantages have resulted in high reliability and long life expectancy, greater battery efficiency, elimination of need for warm-up time, and much smaller size. Also, the transistor adapts well to the low-voltage, low-resistance, high-current circuits necessary for artificial cardiac stimulation.

Method of Operation.—The battery used in this pacemaker is a 9.4-volt mercury battery. This battery has a high capacity-to-size ratio and flat voltage-discharge curve, so that for a given setting of the pacemaker stimulation is relatively constant throughout the useful life of the battery. The pacemaker output chosen was a 2-msec. square wave-current pulse, variable in amplitude from 1 to 20 ma. into a 1,000-ohm load. A 2-msec. pulse length was used, since this is far enough out on the strength-versus-duration stimulation curve to evoke a systole with a reasonably small current and yet far short of that capable of triggering ventricular fibrillation. A special blocking oscillator transformer was developed to secure the proper pulse width at the voltage used and yet have a low core loss. Because experience has shown that heart circuit resistances seldom run below 350 ohms, the pacemaker is calibrated in milliamperes for this load plus a liberal margin, since it is current density at the cathodal lead that initiates a self-propagating excitation wave in the myocardium. The blocking oscillator repetition rate is variable from 60 to 180 pulses per minute. A neon flasher is incorporated on the face of the pacemaker to indicate the stimulating pulse frequency.

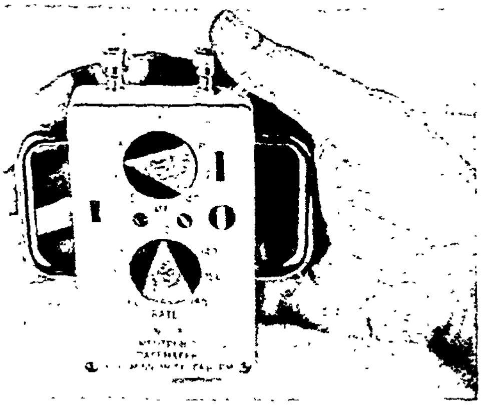

Fig. 1.—Transistor pacemaker with self-contained battery for use in treatment of complete atrioventricular dissociation.

Location of Electrodes.—The pacemaker stimulus is delivered directly to the heart by means of an electrode implanted in the ventricular myocardium. This myocardial electrode is a braided tantalum (or stainless steel) wire (copper wires being less satisfactory because of fatigability and increased reaction about the electrode) insulated with polytetrafluoroethylene (Teflon). A semicircular needle, swedged onto the end of the wire, facilitates rapid and easy insertion. The electrode is anchored in the myocardium with several silk sutures; the wire is brought out through a tiny stab incision in the chest wall and connected to the negative pole of the pacemaker. A flat metallic electrode is inserted into the subcutaneous tissue of the chest wall and connected to the indifferent pole of the pacemaker (fig. 3, *top*). An alternative method, frequently used, has been bipolar stimulation by means of two myocardial electrodes, in which case the indifferent electrode is unnecessary (fig. 3, *center*). More recently a bipolar electrode, as a single unit, with the two terminals 5 mm. apart, has been developed (fig. 3, *bottom*). This is advantageous when long-term stimulation is contemplated, since only a single small wire needs to emerge through the chest wall. We also use this single bipolar electrode routinely now in our surgical patients.

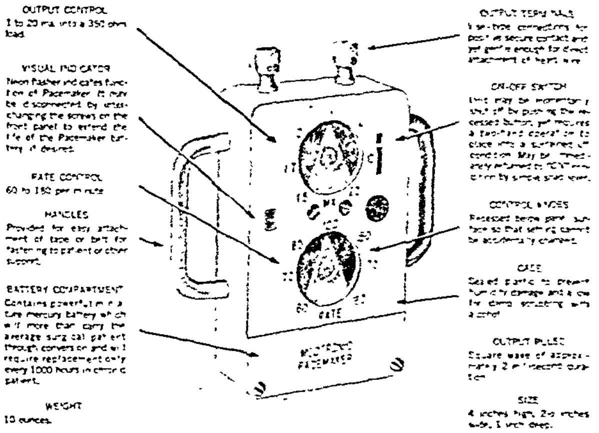
OUTPUT CONTROL
1 to 20 ma. into a 350 ohm load.
VISUAL INDICATOR
Neon flasher indicates function of Pacemaker. It may be disconnected by interchanging the screws on the front panel to extend the life of the Pacemaker battery if desired.
RATE CONTROL
60 to 180 per minute
HANDLES
Provided for easy attachment of tape or belt for fastening to patient or other support.
BATTERY COMPARTMENT
Contains powerful miniature mercury battery which will more than carry the average surgical patient through convalescence and will require replacement only every 1000 hours in chronic patient.
WEIGHT
10 ounces.
OUTPUT TERMINALS
Vise-type connections for positive secure contact and yet gentle enough for direct attachment of heart wire.
ON-OFF SWITCH
Unit may be momentarily shut off by pushing the recessed button, yet requires a two-hand operation to place into a sustained off condition. May be immediately returned to "ON" position by simple slide lever.
CONTROL KNOBS
Recessed below panel surface so that setting cannot be accidentally changed.
CASE
Sealed plastic to prevent humidity damage and allow for damp sterilizing with alcohol.
OUTPUT PULSE
Square wave of approximately 2 millisecond duration.
SIZE
4 inches high, 2½ inches wide, 1 inch deep.
RATE

Fig. 2.—Diagram describing details of pacemaker design, construction, and operation.

In our experimental work there have been no appreciable differences in demand for current or cardiac function with regard to whether unipolar or bipolar ventricular stimulation has been used. It appears that in patients the ventricles are slightly more responsive to bipolar as compared to unipolar stimulation and slightly more responsive to endocardial as contrasted with myocardial stimulation. While it should be obvious that in the presence of complete heart block the electrode must be placed within the ventricular myocardium, it makes no difference[6] where in the ventricles the electrode(s) is implanted. Thus, the right ventricle is usually chosen as the most convenient site, and in surgical

TRANSISTOR PACEMAKER FOR TREATMENT OF COMPLETE ATRIOVENTRICULAR DISSOCIATION

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The pacemaker here described has been used in 66 patients to correct complete heart block. In most cases the block followed surgical procedures, but it also occurred in some nonsurgical patients. The pacemaker consists of three parts: a 9.4-volt mercury cell battery as the source of power; a transistorized oscillator transformer to generate the pulses needed to stimulate the heart; and a unipolar or bipolar electrode in the form of a wire anchored by stitches to the myocardium. The myocardium of the right ventricle has usually been chosen as the most convenient site. Nonsurgical patients incapacitated by complete heart block with low cardiac output have had their conditions maintained on continuous stimulation for up to 15 months by means of this equipment.

A *transistor* pacemaker (fig. 1) and bipolar electrode has been developed for use in patients with complete atrioventricular dissociation and an inadequate cardiac output. This pacemaker is designed for either short-term or long-term ventricular stimulation by means of an internally implanted myocardial electrode.[1]

Complete atrioventricular dissociation is likely to occur in about 10% of patients who have undergone surgical repair of septal defects located in the vicinity of the atrioventricular node and the common bundle of His, and this method of internal stimulation was developed originally to meet this need.

Temporary or permanent complete heart block is not, however, a rare complication of many diverse types of myocardiopathy, sometimes idiopathic or induced by arteriosclerosis, infection, or drug administration; therefore this method of internal stimulation has found a place also in the treatment of selected patients with complete block from these causes.

At first the significance of surgically induced complete heart block rested in its high mortality. Of the first seven patients with septal defects in whom this complication of open-heart surgery developed in 1954-55, all died in the immediate postoperative interval despite the use of epinephrine, ephedrine, atropine, sodium lactate, and the external electric pacemaker; death was clearly a result of an insufficient cardiac output owing to the acutely slowed ventricular rate. The condition was further aggravated by the increased metabolic needs in the immediate postoperative interval, so that cardiac rates below 70 per minute were usually incompatible with life. Moreover, as we have previously pointed out [1a] the widespread adoption by many surgeons of the practice of arresting the heart with potassium citrate and prolonged anoxia during surgical repair of septal defects significantly increases the incidence of complete heart block.

Attention then turned to the use of isoproterenol hydrochloride,[2] and this drug was effective in reducing the mortality to about 40% by increasing cardiac rhythmicity and rate.[3]

Treatment was not satisfactory, however, until the combined use of an electric pacemaker and a fine electrode implanted into the heart muscle was developed.[4] The ventricles in block are very responsive to repetitive electric stimuli, and only low currents, which are imperceptible to the patients, are needed. With this treatment the mortality of heart block occurring as a complication of cardiac surgery has fallen greatly, and this, together with other developments, has been one of the important factors reducing the over-all risk of operation for septal defect to low levels.[5]

In addition, a simple technique has recently been developed for *percutaneous* insertion of a myocardial electrode [1a] which should prove equally lifesaving for certain nonsurgical patients with this problem and in whom emergency treatment may be required.

Advantages of Internally Implanted Transistor Pacemaker

The pacemaker is compact, being only slightly larger than a package of cigarettes. Its small size, light weight, and self-contained power source allow for complete patient mobility. A light, washable shoulder "holster-type" sling, made of cotton with snap fasteners, has been developed to allow ambulant patients who require continuous stimulation to wear their pacemaker conveniently while leading an active life. Because it is battery-operated, patient safety and efficiency of patient care are greatly improved. The patient is not in danger of electrocu-

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From the Department of Surgery and the Variety Club Heart Hospital, University of Minnesota Medical School.

the resistance through the electrode gradually rose to about 500 ohms in the first six weeks and has not changed appreciably since.

In another patient, a 38-year-old engineer who was unable to work since 1957 because of idiopathic heart block and is now able to return to work, the resistance measured through his bipolar electrode six days after insertion was 230 ohms and the heart was driven by less than 2.5 ma. One month later, these measurements were 366 ohms and less than 3 ma. respectively.

Comment

Since the initial description of a patient with complete heart block after closure of a ventricular septal defect who, in 1957, was successfully treated by use of a myocardial electrode and an artificial pacemaker,[6] this method has been universally adopted by cardiac surgeons faced with this complication.

The miniaturized equipment here described, as well as the bipolar electrode, has been thoroughly tested and found to facilitate the use of this method by increasing safety and reliability and by providing the possibility of ambulatory treatment. The latter advantage has been particularly useful in extending the benefits of this form of treatment to those nonsurgical patients who sustain complete heart block secondary to coronary arteriosclerosis, drug therapy, or one of the other diverse causes of Stokes-Adams syndrome. In these persons the indication for use of electrical stimulation has been limited to those who are incapacitated despite the conventional forms of medical treatment by either intermittent attacks of syncope or a cardiac output which remains consistently so low that useful work and physical activity have become impossible. Not only has the threat of sudden death in these patients been removed, but their physical and emotional rehabilitation has been dramatic. Further miniaturization of equipment for such patients is entirely feasible. Moreover, experimental work in dogs has indicated the feasibility of implantation of a tiny coil within the myocardium and the use of electromagnetic waves through the intact chest wall from a transmitter on the skin surface. This latter method of stimulation by electromagnetic induction has not yet reached the state of practicality necessary for clinical use.

With regard to the clinical use of direct myocardial stimulation, two facts are worthy of mention. First, the ventricles with a reduced cardiac output due to a slow rate secondary to complete atrioventricular dissociation respond extremely well to repetitive electric stimuli of small magnitude delivered directly to the myocardium. On the other hand, an inadequate cardiac output due to a failing myocardium, e. g., from anoxia or any of innumerable causes, will not respond to electrical stimuli. Even though complete heart block may be present in such patients, it is clearly secondary to the cause of the myocardiopathy and not the primary problem.

Secondly, in patients in whom complete block is the primary problem, even though the heart rate and cardiac output are readily restored to adequate levels by internal stimulation, the fact that the induced ventricular and the natural atrial contractions are asynchronous means that the heart is less efficient than it would be under comparable conditions with normal sinus rhythm. This reduction in efficiency is not great but it is similar to that which occurs with atrial fibrillation and has been estimated to be about 15%. In the usual patient this reduction is not significant because of the large reserve that exists. In a few surgical patients with complete heart block, however, such as those with a ventricular septal defect and severe pulmonary hypertension due to extensive arteriolar vascular narrowing or in patients with tetralogies with a very hypoplastic pulmonary artery, this reduction in cardiac efficiency might be a decisive factor in the immediate postoperative interval before readjustments have had time to occur. Thus, we have considered the possibility of using the patient's own P wave to trigger the ventricular stimulus, according to a system which has been described.[4] The practical difficulties, aside from the additional complexity of the equipment needed, have been due to the fact that, in the immediate postoperative interval when such a method has its greatest value, the P-wave rate is often unreliable, showing extremes in both directions. For the more usual patient, therefore, use of a P-wave pick-up and amplification to synchronize atrial and ventricular contractions does not seem necessary.

The question of how long stimulation can be maintained appears to be related to electrode materials, design, and technique of implantation. Suffice it to say that, with the present electrodes, continuous stimulation for periods well over one year has been achieved, without appreciable increase in the impedance after the first six weeks. Since these patients are still under stimulation, it is not possible to provide, at this time, an estimate of the average functional interval to be expected with a single electrode. If an electrode does fail, another may be implanted. We recently have implanted two of the single bipolar electrodes in nonsurgical patients in whom long-term stimulation is anticipated. One is brought out through the skin immediately to be used for stimulation, and the other is left buried in the subcutaneous tissue where it can be easily located should the first fail.

The possibility of infection along the wire exists, but we believe that this danger can be minimized by tunneling the wire for some distance before bringing it out through the skin.

patients the diaphragmatic surface of the right ventricle away from the cardiotomy incision is recommended.

In medical patients or in other emergency situations, pacemaker stimulation can be instituted by percutaneous insertion[14] of a wire in the myocardium. Insulation of the electrode is not necessary. However, where long-term stimulation is contemplated, we believe it is preferable to expose a small area of the right ventricle myocardium and insert an insulated bipolar electrode directly. This may be done by means of a small incision in the fourth interspace just to the left of the sternum, with the patient under local anesthesia, without entering the pleura.

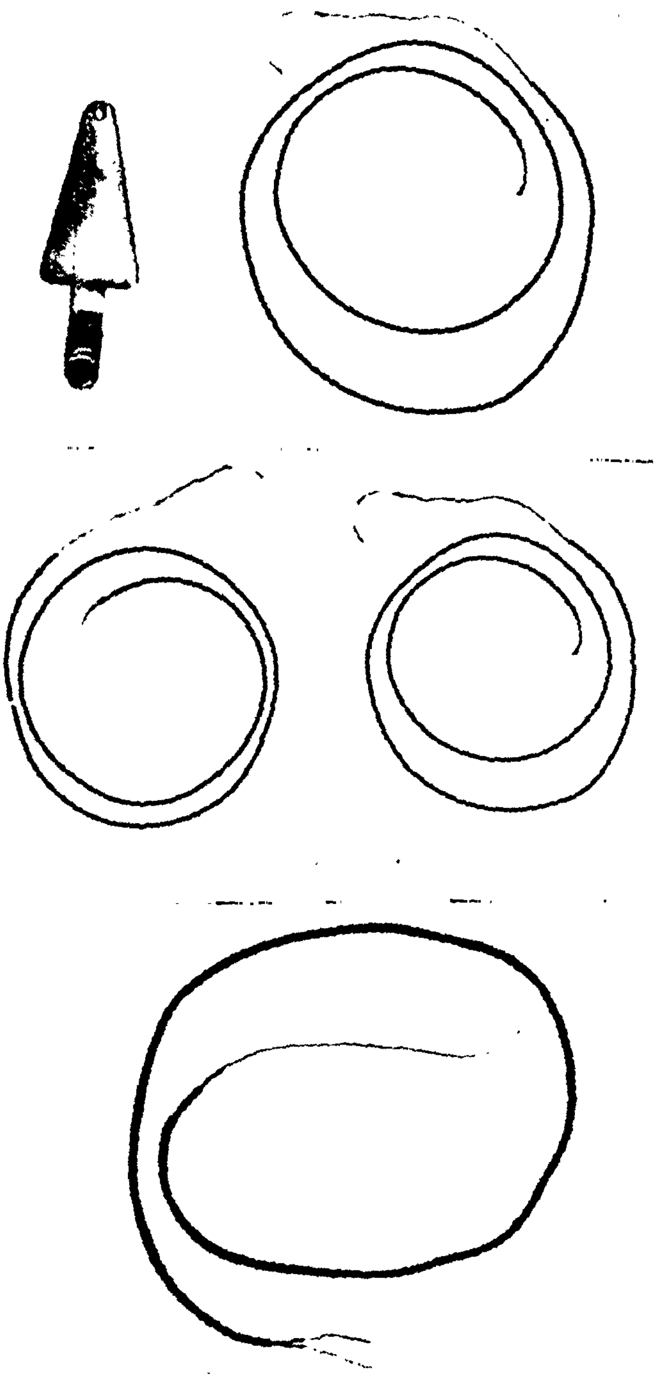

Fig. 3.—Myocardial electrodes used with pacemaker for direct cardiac stimulation. *Top*, braided tantalum electrode with Teflon insulation. Swedged-on needle facilitates implantation into myocardium, after which needle is cut off and electrode wire secured in place with several silk stitches. Triangular indifferent electrode is placed subcutaneously in thorax over left apex beat as indifferent electrode. *Center*, alternative method of bipolar stimulation, with use of two electrodes implanted directly into myocardium. *Bottom*, recently developed bipolar electrode combined into single unit. End implanted into myocardium has two terminals, 5 mm. apart. Swedged-on needle facilitates implantation, after which excess distal wire is cut off flush with myocardial surface. This electrode consists of two fine braided stainless steel wires coated individually with polytetrafluoroethylene insulation and then combined into single sheath of a nonreactive silicon plastic (Silastic).

Timing and Degree of Stimulation.—In cardiac surgical patients, the electrode is inserted without delay at the time of thoracotomy if complete atrioventricular dissociation is noted or even suspected. If complete block is obvious, it has proved advantageous to institute stimulation before taking the patient off the heart-lung machine. The pacemaker stimulus is used as long as the patient remains in complete heart block. The rate of stimulation is usually 100 to 120 per minute, or roughly equivalent to what the patient would be expected to have under similar conditions were complete heart block not present.

About two-thirds to three-fourths of the surgical patients regain sinus rhythm within the first two to three weeks of continuous electrical stimulation. When the patient reverts to sinus rhythm, the pacemaker is turned off and careful monitoring of the pulse rate is instituted. (A companion transistorized monitor, with alarm, has been developed. This monitor uses the myocardial electrode to augment sensitivity and reliability. The monitor is inserted into the same circuit with the pacemaker to activate the pacemaker automatically should the patient's rate suddenly fall below a predetermined level.) After several days, if sinus rhythm has been maintained, the myocardial electrode is removed by gentle traction.

Those surgical patients who remain in complete block after this time may usually be weaned from the pacemaker gradually by progressive lowering of the rate of stimulation, supplemented by use of rectally or orally given isoproterenol hydrochloride as previously described.[7] If other factors indicate a need, there is no contraindication to the use of digitalis in patients on pacemaker stimulation.

The transistor pacemaker in combination with the myocardial electrode has been used in 66 patients at the University of Minnesota Hospitals to date. Most of the patients have had complete heart block secondary to surgical procedures, but an increasing number of nonsurgical patients with Stokes-Adams syndrome have been restored to useful activity.

The longest interval of continuous stimulation of a patient's heart by means of a bipolar electrode and the equipment herein described has been 15 months. This patient is still under stimulation, and

STUDY OF INCIDENCE OF ABDOMINAL AORTIC ANEURYSM IN NEW ORLEANS

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Because of the interest in abdominal aortic aneurysm the autopsy records of all hospitals and the Coroner's Office of the New Orleans area were reviewed for the years 1947 to 1957 in order to obtain an impression of its incidence. In 26,554 autopsies performed during this 10-year period, 158 (0.6%) abdominal aortic aneurysms were found. Sixty-three percent of the 158 aneurysms were intact, 28% had ruptured or dissected spontaneously, and in 9% of the cases immediate postoperative death had resulted from resection of the aneurysm. During the last three years of the study (the period when surgical intervention became popular in this area), 60% of the aneurysms were intact at autopsy, 13% had ruptured spontaneously, and in 27% of the cases immediate postoperative death had resulted from resection of the aneurysm.

Aneurysms of vascular structures have been recognized for centuries, being mentioned in the Ebers papyrus.[1] Antyllus (c. 150 A. D.) classified aneurysms and described many details of their treatment.[1] His therapeutic techniques were used, essentially unchanged, until the time of John Hunter, 16 centuries later. Ambrose Paré suggested the etiological relationship between syphilis and aneurysm formation. Lancise consolidated the then existing knowledge of aneurysms in his treatise, "De Moto Cordis et Aneurysmatibus" (1728). He, like Paré, also recognized the "aneurysma gallicum." Vesalius was the first to give a clinical description of an abdominal aortic aneurysm.[2] By the 19th century the literature dealing with aneurysms had become so extensive that Erichsen was able to collect 150 comprehensive publications on the subject.[3] Aneurysms of the aorta have received considerable attention in the present century, and some reports[4] suggest that abdominal aortic aneurysm is a frequently encountered disease entity. Because this did not seem to be supported by personal experience, it was considered of interest to learn the incidence of aneurysm of the abdominal aorta in the New Orleans area by a study of all autopsies performed in this city for a consecutive 10-year period. Such a study is also important in evaluating abdominal aneurysm as a public health problem.

Material and Method

The records of all autopsies performed in six metropolitan New Orleans hospitals during a 10-year period (1947-1957) (table 1), and all of the Orleans Parish coroner's autopsy records for a 7-year period (1950-1957) were reviewed. This study, therefore, included all autopsies performed in the New Orleans area for the years indicated. Clinical records were not studied because of possible errors in clinical diagnosis.

Results

The incidence of abdominal aortic aneurysm for the six hospitals is shown in table 1. The high incidence for the New Orleans Veterans Administration Hospital, 1.9% of all autopsies, probably reflects the preponderance of men and the higher age of the patients in this hospital. Of the 44,354 deaths in the six hospitals studied, 21,139 were investigated by autopsies (47.6%). During a seven-year period there were 26,720 coroner's cases, with 5,415 autopsies (20.3%). This study, therefore, includes 26,554 autopsies from seven sources.

In this series of 26,554 autopsies, 158 abdominal aortic aneurysms were found (about 16 abdominal aneurysms per year for all autopsies performed in the New Orleans area), an incidence of 0.6% or essentially one of every 168 autopsies (table 2). Of these aneurysms 62.6% were found to be intact at autopsy, 24.7% had ruptured, 3.8% had dissected, and of the 158 patients with aneurysms, 8.9% were classified as immediate postoperative deaths. Twenty-four per cent of the 158 patients had positive serologic findings, and 59% had arterial hypertension at the time of death. The age distribution of the patients is shown in figure 1. Table 2 compares the data of this study with those of other investigators. Table 3 summarizes the sex and racial incidence for the 158 abdominal aneurysms of this study, the incidence being almost three times more frequent in white than in Negro persons and at least three times more frequent in men than in women.

From the Department of Medicine, Tulane University School of Medicine, the Charity Hospital of Louisiana, and the Veterans Administration Hospital.

Summary

In complete heart block the ventricles are extremely responsive to repetitive electrical stimuli of small magnitude delivered by an electrode implanted in the ventricular myocardium. This method has proved to be the most effective method of managing this complication of open-heart surgery and has been universally adopted by cardiac surgeons.

A light-weight transistorized pacemaker, with a self-contained battery of long life, has been developed to facilitate continuous electrical stimulation of the heart. This pacemaker may be worn by the patient, making ambulatory treatment practical. Safety to the patient has been increased by this unit, since sources of difficulty due to power failure or electrocution due to short circuits are obviated by the use of a battery power source.

A single bipolar braided stainless steel electrode, with good duration of function characteristics, has also been described.

Nonsurgical patients incapacitated by complete heart block with low cardiac output have been maintained on continuous stimulation for up to 15 months by means of this equipment. It would appear that a small portable pacemaker such as the one herein described may improve the prognosis of many patients afflicted with incapacitating complete atrioventricular dissociation associated with an otherwise adequate myocardium. Various refinements and improvements of this equipment are possible, feasible, and under study.

This study was supported by research grants from the graduate school of the University of Minnesota; the Minnesota Heart Association; the Life Insurance Medical Research Fund; the National Heart Institute; donors to Minnesota Surgical Research Fund and the Anthony R. Barnett Memorial Fund.

Mr. C. W. Norman supplied the braided tantalum and stainless steel electrodes with swedged-on needles. The polytetrafluoroethylene insulation was supplied as Teflon by Medtronic Laboratories, Inc., Minneapolis 818, who manufactured the pacemaker, cardiac alarm, and electrodes used in this study.

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THE DEGREE OF PREMATURITY.—As more attempts are made to follow the course of development of prematurely born children, a clearer understanding is obtained of their position relative to their full-term contemporaries. . . . The present report compares the neurological and intellectual status of a group of 460 prematurely born children examined at 3 to 5 years of age with that of a matched group of 440 full-term children serving as controls. The findings at this examination are related to similar data pertaining to the same children obtained when they were 40 weeks of age. At both examinations the prematurely born group was found to rate somewhat lower in intellectual status and to have a smaller proportion classed as neurologically normal than the full-term children. When the prematures were subdivided by birth weight the trend favoring those with larger birth weights was maintained. For example, those in the group with birth weights from 2,001 to 2,500 grams were only slightly different from the controls; those whose birth weights were under 1,501 grams were more seriously handicapped. Consequently, a statement about "prematures" is more useful when details regarding degree of prematurity are available.—P. A. Harper, M.D., L. K. Fischer, Ph.D., and R. V. Rider, Sc.D., Neurological and Intellectual Status of Prematures at Three to Five Years of Age, *The Journal of Pediatrics*, December, 1959.

26,554 autopsies. If this is representative of the entire country, then investigation of the total deaths in the United States for 1957 would have demonstrated 9,799 abdominal aortic aneurysms. If 25% of these aneurysms ruptured spontaneously, it can be extrapolated that essentially 2,450 abdominal aortic aneurysms rupture in the United States of America per year. In 1957 there were 452,507 deaths in the United States due to arteriosclerotic heart disease, 72,372 deaths due to hypertensive cardiovascular disease, and 19,274 deaths due to chronic rheumatic fever.[7]

It is also of interest to compare mortality in the United States from certain cardiovascular and renal diseases for 1947 and 1957 to determine if any trends exist.[8] Deaths from arteriosclerotic heart disease and cerebrovascular accidents have increased, whereas deaths from hypertensive heart disease, chronic nephritis, diabetes mellitus, chronic rheumatic heart disease, syphilis, chronic and acute endocarditis, and syphilitic aortic aneurysm have decreased. The decrease in deaths from syphilitic aortic aneurysm is unquestionably the result of effective antibiotic therapy. Deaths from nonsyphilitic aortic aneurysm (thoracic and abdominal) have increased, as have deaths from congenital heart disease. The great increase in deaths from aortic aneurysm (376%), although still only 0.4% of all deaths for 1957, is probably a result of several factors, including better diagnosis and the over-all trend toward an increased incidence of arteriosclerosis.

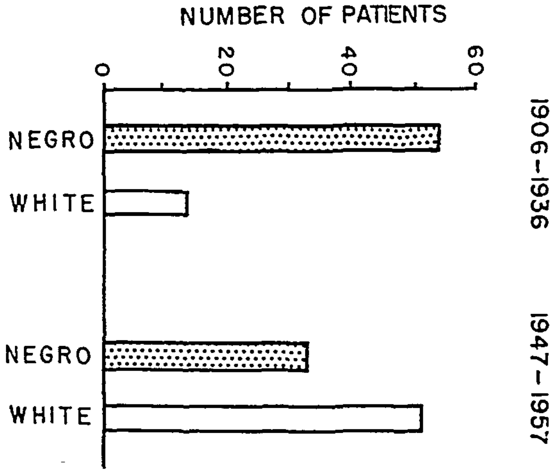

Fig. 2.—Comparison of racial incidence of abdominal aortic aneurysm at Charity Hospital in New Orleans for 1906 to 1936[9] and 1945 to 1957 (present study).

Summary

Results of a study of the autopsy records of six metropolitan New Orleans hospitals and of the Orleans Parish coroner's office for the incidence of abdominal aortic aneurysm were as follows: In 26,554 autopsies, only 158 aneurysms of the abdominal aorta were found, an over-all incidence of 0.60%. Of the 158 aneurysms, 62.6% were intact at the time of autopsy, 24.7% had ruptured, 3.8% had dissected, and in 8.9% of the cases surgical removal of the abdominal aneurysm resulted in postoperative deaths.

During the last three years of this study (period of surgical intervention) 60% of the aneurysms were intact at the time of autopsy, 13% had ruptured, and in 27% of the cases abdominal aneurysm was removed, resulting in postoperative death.

1430 Tulane Ave. (12) (Dr. Burch).

This study was supported by grants from the U. S. Public Health Service and the Thibodeaux Foundation.

The administrators and physicians of Charity Hospital, Veterans Administration Hospital, Touro Infirmary, Southern Baptist Hospital, Mercy Hospital, and the New Orleans Coroner's Office provided assistance in the execution of this study and permission to use the autopsy records of their respective institutions.

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Comment

In this series of 26,554 autopsies, 158 abdominal aortic aneurysms were found. Rupture or dissection of the aneurysm accounted for only 39 (0.15%) of these 26,554 deaths, or about 1 per 700 autopsies. One-fourth of the 158 abdominal aneurysms found at autopsy had ruptured spontaneously; however, the autopsies for the last three years (the period after surgical intervention became popular) of this study, revealed that 27% of the deaths from aneurysms were classified as operative and that the incidence of death due to spontaneous rupture was 13%.

TABLE 1.—*Survey of Abdominal Aneurysms at Six Metropolitan New Orleans Hospitals, (1947-1957)*

				Abdominal Aneurysms		
Hospital	Total Admissions	Total Deaths	Total Autopsies	No. at Autopsy	% of Total Admissions	% of Total Autopsies
Charity	675,606	28,304	11,124	84	0.010	0.59
VAH	44,562	2,083	1,651	32	0.070	1.94
Mercy	91,474	1,840	527	3	0.003	0.56
Hôtel Dieu	140,708	3,266	1,058	10	0.007	0.94
Touro	173,613	4,182	2,272	10	0.006	0.44
Baptist	253,398	4,899	1,507	5	0.002	0.33
Totals	1,382,391	44,574	21,139	144	0.010	0.68

Kampmeier[5] conducted a similar study of the incidence of abdominal aneurysms at the Charity Hospital in New Orleans for the years 1906-1936.

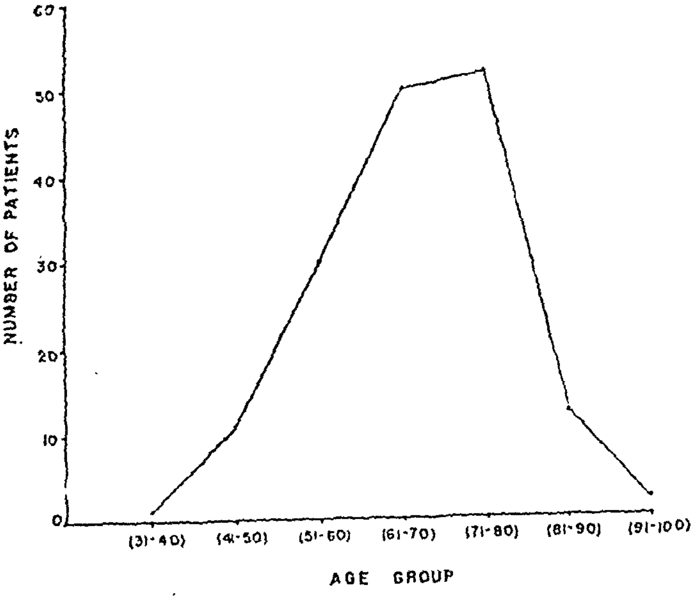

Fig. 1.—Age distribution of 158 patients with abdominal aortic aneurysm observed at autopsy.

He found that most patients with abdominal aortic aneurysm were Negroes, whereas in the present study the opposite was found to be true for the same hospital for the years 1947 to 1957 (fig. 2). The incidence of abdominal aneurysm was slightly greater in this latter series. At the Charity Hospital, between 1906 and 1936, there were more deaths and autopsies among the white population than among the Negro population, whereas between 1947 and 1957 (this study) there were slightly more autopsies among the Negro than the white population. This would indicate that the greater number of abdominal aneurysms seen in Negro persons for the years 1906 through 1936 was real rather than due to the characteristics of the sample. This also reflects a trend which had been pointed out previously, i. e., that the incidence of syphilitic aneurysm has decreased and that the relative and absolute incidence of arteriosclerotic aneurysm has increased. Perhaps, in time, with an aging population, arteriosclerotic abdominal aortic aneurysm will become a somewhat more common disease, as some reports suggest.[4c]

TABLE 2.—*Incidence of Abdominal Aortic Aneurysms Based on 117,348 Autopsies*

Source	No. of Autopsies	No. of Abdominal Aneurysms	% of Autopsies
Bryant[9]	18,678	54	0.29
Osler[2]	2,200	11	0.50
Lucke and Rea (9)[10]	12,000	40	0.33
Genert[11]	1,062	6	0.56
Ogden[12]	9,000	15	0.17
Ruffin and others[13]	9,600	20	0.21
Maniglia and Gregory [4c]	6,000	31	0.52
Kampmeier[5]	12,053	38	0.31
Sommerville and others[6]	20,201	178	0.88
This series	26,554	158	0.60
Totals	117,348	551	0.47

A recent review of 20,201 autopsies by Sommerville and co-workers[6] yielded 178 abdominal aneurysms, an incidence of 0.9%. Of these 178 aneurysms 31 had ruptured, so that of 20,201 deaths 0.15% were due to rupture of an abdominal aortic aneurysm. This figure is essentially the same as that found in the present study wherein of a total of 26,554 autopsies, death was due to ruptured aneurysms in 0.15% of the cases.

TABLE 3.—*Age, Sex, and Race of 158 Patients with Abdominal Aneurysms at Autopsy*

	Race			
	Negro		White	
Age Group, Yr.	Men	Women	Men	Women
30-40......................	0	1	0	0
41-50......................	5	2	3	1
51-60......................	8	1	16	5
61-70......................	11	4	28	7
71-80......................	5	4	37	6
81-90......................	1	1	7	3
91-100.....................	0	0	2	0
Totals	30	13	93	22

Certain rough calculations regarding the incidence of abdominal aortic aneurysm for the nation as a whole are of interest. For example. 1,633,128 deaths in the United States this study 158 aneury [illegible] re but anorexia and occasional vomiting continued. For the three days preceding admission the baby had been increasingly weak, lethargic, and restless.

On admission the patient appeared extremely dehydrated and in a moribund condition, being both acutely and chronically ill; he was lethargic and cried weakly only after severe stimulation. Turgor of the skin was poor, his eyes were sunken, and his respirations were rapid and shallow. The liver was palpable 3.5 cm. below the costal margin; it was nontender and its surface was smooth. There were no other physical findings of note.

A blood sample was obtained before the initiation of intravenous fluid therapy (table 2); the serum chloride and sodium concentrations were extremely low, while at the same time the serum pH was markedly elevated. The serum potassium concentration was not measured at this time, but later the same day it was 3.03 mEq. per liter after one and three-quarters hours of intravenous administration of isotonic sodium chloride solution. By the next day the patient had improved considerably, but the serum potassium concentration had decreased to the low level of 1.9 mEq. per liter. Potassium chloride was therefore added to the solution being given intravenously, after which recovery was uneventful. After 48 hours intravenous therapy was discontinued and oral feedings resumed.

TABLE 1.—*Clinical and Diagnostic Data on Five Patients with Cystic Fibrosis of Pancreas (CFP)**

Case No.	Age and Sex	Family History of CFP	Involvement		Tryptic† Activity of Duodenal Contents	Electrolytes in Sweat (mEq./L)		Date of Admission	Reason for Admission	Symptoms Prior to Admission		Status Present
			Pulmonary	Intestinal		Chloride	Sodium			Vomiting	Diarrhea	
1	4 mo., M	Yes	+	+	0	200	182	4-12-54	Severe dehydration	Occasional for 15 days	Occasional	Doing well since 1954
2	7 mo., M	No	±	+	0	127	114	4-12-55	Dehydration	Moderate for 3 days	None	Doing well since 1955
3‡	14 mo., M	No	++	++	0	95	89	12-4-57	Severe dehydration	Twice a day for 2 days	None	Doing well since 1958
	16 mo.	No	++	++	—	102	108	2-1-58	Severe dehydration	Moderate for 4 days. Not taking fluids	None	
4	6 wk., M	No	+++	++	—	77	124	9-25-56	Examined for adrenal insufficiency	Regurgitation for 3 wk. Hypoelectrolytemia	None	Died of pulmonary complications, 1956.
5	4 wk., M	No	±	+	0	91 108	79 93	2-18-57	Examined for adrenal insufficiency	Occasional vomiting	None	Doing well since 1957

* All patients were caucasoid.
† Method of Northrop and Hussey: viscosimetric units normal >100 u/cc.
‡ This patient had 2 hospital admissions.

An electrocardiogram made on April 14, 1954, at a time when the serum potassium concentration was still low, showed changes in the T waves compatible with hypopotassemia.

Subsequent investigations carried out at a time when the patient was in electrolyte equilibrium confirmed the diagnosis of fibrocystic disease of the pancreas. Duodenal juice showed no tryptic activity, and roentgenography of the chest demonstrated the presence of generalized obstructive emphysema, without secondary bronchopneumonic changes. At a later date a "sweat test" showed the sweat chloride level to be 200 mEq. per liter and the sweat sodium level 182 mEq. per liter, both markedly above normal and typical of this disease.

In order to rule out a renal or adrenal basis for the hypoelectrolytemia the patient was given a form of powdered whole milk containing little sodium (Lonalac) and his urine was collected in three 24-hour periods. The results (see figure) indicated excellent conservation of sodium by the kidney, a total of only 2 mEq. being excreted in the urine in 24 hours on the third day of salt restriction.

The patient's mother had been on a "salt-poor" diet for many years because of preceding rheumatic heart disease. Since the patient had been breast-fed, with few other foods added, it was believed that this might be of causal significance. Therefore, the electrolyte content of the mother's breast milk was determined on two subsequent days (table 3). The chloride, sodium, and potassium concentrations in the breast milk of a normal control mother, who did not have children with cystic fibrosis, was assayed simultaneously.

Surprisingly, the sodium and chloride levels in the patient's mother's breast milk were much increased, when compared with normal values obtained from the literature, with our own control, and with the figures reported by Rendle-Short[2] for the mother of a patient with cystic fibrosis. The potassium levels were not increased in the patient's mother's breast milk, a fact which had been found true of other secretions of exocrine glands in patients with cystic fibrosis.[3]

CASE 2.—A 7½-month-old boy was admitted to Babies' Hospital for the first time on April 22, 1955, in severe dehydration. There were no siblings and the family history was noncontributory, except for

SALT DEPLETION IN COLD WEATHER IN INFANTS WITH CYSTIC FIBROSIS OF THE PANCREAS

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Infants with cystic fibrosis of the pancreas are susceptible to salt depletion and dehydration even in cold weather. Five such infants, ranging in age from 4 weeks to 16 months, were admitted to Babies' Hospital over four years for treatment of hypoelectrolytemia and for study of the underlying cause. All had some vomiting not thought to be sufficient to explain the symptoms. One had slight diarrhea preceding admission; the other four had none. Repeated, small excessive losses of electrolytes in sweat and possibly in gastric secretion leading to negative salt balance over a period of time appeared to be factors in the genesis of the clinical picture. Cystic fibrosis of the pancreas should be kept in mind in the differential diagnosis of hypoelectrolytemia and dehydration in infancy. When this disease is suspected, salt supplements should be added to the diet, even in cold weather.

Patients with cystic fibrosis have abnormally high levels of electrolytes in sweat, and it is recognized that they are prone to develop salt depletion as a consequence of sweating in the summer heat, with serious and at times fatal consequences.[1] It is not generally realized, however, that children and especially infants with cystic fibrosis are susceptible to salt depletion and dehydration in circumstances other than a hot environment. Up to this time, to my knowledge, with the exception of a case described by Rendle-Short,[2] no patients have been reported in the literature in whom this picture obtains in cool or even cold weather. Their recognition has important diagnostic and prophylactic implications. The object of this paper is to report on five such patients and to bring this problem to the attention of the medical public.

Patient Material

Five patients with cystic fibrosis, ranging in age from 4 weeks to 16 months, were admitted to Babies' Hospital over a period of four years for treatment of hypoelectrolytemia or for study of the underlying problem (table 1). The patients in cases 1, 2, and 3 were admitted because of severe dehydration; those in cases 4 and 5 were referred by an outside hospital shortly after the acute episode, with a tentative diagnosis of adrenal insufficiency. All had some vomiting, not thought to be sufficient to explain the symptoms. Diarrhea had been absent in all. With the exception of the patient in case 3, none of the infants included in this report was known to have cystic fibrosis before admission, the diagnosis not even being suspected. It was felt that none of their preceding symptoms was sufficient to explain the hypoelectrolytemia and dehydration, the mechanism of which remained unexplained.

In tables 1 and 2 are listed some of the pertinent laboratory and clinical data. The figure shows graphically the results of studies performed in three of these patients (cases 1, 3, and 5) in order to evaluate further the conservation of sodium by their kidneys.

Report of Cases

Case 1.—A 4-month-old boy was admitted for the first time, severely dehydrated and *in extremis,* on April 12, 1954. The father was well, but the mother had a history of rheumatic heart disease in childhood. Two siblings of the patient had died, several years previously, of fibrocystic disease of the pancreas, proved at autopsy in one case. Four other siblings, all female, were living and well.

The patient had a normal spontaneous delivery and a normal neonatal period. He had been breast-fed, with supplementary feedings of evaporated cow's milk. Vitamins had been administered regularly, and more recently cereal and egg yolk had been added to the baby's diet. The patient's appetite had been always good and his stools unremarkable.

Two weeks before admission the patient had developed a nonproductive cough without fever but did not appear ill. On April 1, 11 days prior to admission, he was placed on therapy with chlortetracycline (Aureomycin). Although his cough improved, he developed abnormal foul, greasy, and bulky stools. He moved his bowels on an average of three times a day. At the same time he lost his appetite and refused all nourishment, with the exception of breast milk. He vomited occasionally, apparently not severely.

After five days chlortetracycline therapy was stopped and penicillin was given by injection. The diarrhea had ceased several days before admission,

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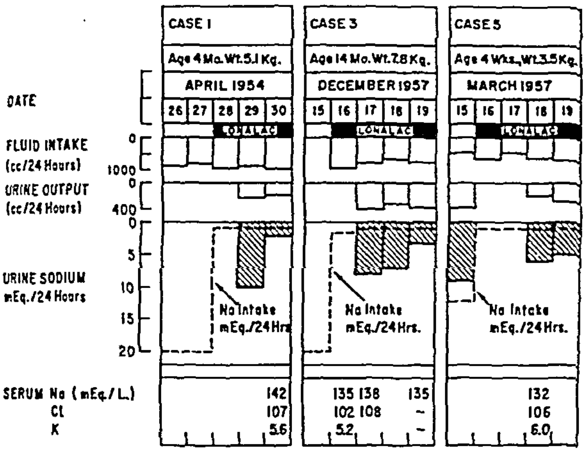
provement after intravenous fluid therapy, and, as can be seen from the figures, within two days the serum electrolyte values were normal.

Because of the history and the finding of marked bilateral obstructive emphysema on roentgenography of the chest, the diagnosis of cystic fibrosis was suspected and subsequently proved by sweat test and duodenal juice assay (table 1). The patient was then discharged on a low-fat high-protein diet, with administration of pancreatic extracts and therapy with antibiotics, and he has subsequently done well, with no further difficulty in his electrolyte balance. He now is on a normal diet with moderate restriction of his fat intake; treatment with antibiotics has been discontinued. On his last visit, April 30, 1959, a roentgenogram of the chest showed no evidence of abnormal changes.



Behavior of sodium in urine of three patients with cystic fibrosis taking salt-free milk (Lonalac).

Case 3.—A 14-month-old boy was admitted to Babies' Hospital in marked dehydration on Dec. 4, 1957. He had previously been given a diagnosis of cystic fibrosis in our hospital, at which time various confirmatory tests were done (table 1). His father and mother and three siblings were living and well. There was no family history of cystic fibrosis.

Two weeks prior to admission the patient had developed anorexia and later had vomited four or five times a day for about five days. In the two days preceding his being brought to the hospital, vomiting had been present only twice daily, but his fluid intake had been poor. Diarrhea had not been present; if anything, the patient had had a tendency to be constipated. Two siblings had experienced abdominal pain and diarrhea preceding the patient's illness.

On admission the patient appeared acutely ill and lethargic and was not crying. His temperature was 101 F (38.3 C). Skin turgor was poor and the anterior fontanel was depressed. His chest was tympanitic on percussion, but there were no rales on auscultation. The rest of the physical examination was noncontributory.

Measurement of serum electrolyte concentrations on admission (table 2) revealed low chloride, sodium, and potassium levels and an increased carbon dioxide combining power. Unfortunately, the pH was not determined. Other blood chemical determinations, blood count, and urinalysis on the next day were within normal limits. Roentgenograms of the chest showed generalized obstructive emphysema, relative microcardia, and bilateral bronchopneumonia.

The patient responded promptly to intravenous administration of fluids, his temperature came down to normal, and by the next morning his condition was much improved, with normal serum electrolyte values.

On Dec. 16, 1957, 12 days after admission, the patient was given a Lonalac formula for four days (see figure) in order to evaluate his renal function as related to sodium chloride intake. His 24-hour urine samples, collected on Dec. 17, 18, and 19, were analyzed for sodium and showed good conservation of salt by the kidneys, a total of only 3 mEq. being excreted in the urine on the fourth day of the study. During the experimental period the patient lost 560 Gm. (19.7 oz.) in weight, but it must be kept in mind that his total caloric intake during the four days of the test was quite low. There were otherwise no untoward symptoms, and on Dec. 19 the serum sodium concentration was 135 mEq. per liter, as it had been prior to the low-salt diet. Three weeks after admission the patient was discharged.

Two months later, on Feb. 1, 1958, he was readmitted in an emergency, extremely dehydrated and almost moribund. Again his siblings had had abdominal pain and sore throat and he himself had been diagnosed by a local physician as having tonsillitis. He had begun to vomit, but only moderately, four days prior to admission, and his fluid intake was poor. He was constipated and had been given three salt-retention enemas the day before being seen. On his way to the hospital he had had a generalized convulsive seizure.

Table 3.—*Electrolyte Levels in Breast Milk of Mothers of Two Patients with Cystic Fibrosis and Controls*

		Breast Milk Electrolytes, mEq./Liter		
Subject	Date	Chloride	Sodium	Potassium
Mother of patient in case 1,* 4 mo. after delivery	4-13-54	34.0	—	—
	4-14-54	33.0	22.8	14.0
Mother of patient reported by Rendle-Short,[2] 3 mo. after delivery	—	12.6	5.9	13.6
Control, 2 mo. after delivery	4-14-54	12.0	3.3	14.8
Controls taken from literature,[3b] 1-4 mo. after delivery	—	10.0	4.8	11.5

* On same day serum electrolyte levels were: chloride, 103; sodium, 143; and potassium, 4.5 mEq. per liter. On May 10, 1954, sweat electrolyte levels were: chloride, 32, and sodium, 35 mEq. per liter.

various manifestations of allergy on both sides of the family. The patient's postnatal weight gain had been unsatisfactory, and malnutrition had always been present, despite an excellent appetite. For the first three months of life he was said to have suffered abdominal pain at frequent intervals, but this had improved in the months preceding admission. He had always had several abnormal foul stools every day but no frank watery diarrhea. Many different formulas had been tried without success, including evaporated goat's milk, which had sparked an episode of infantile eczema.

The patient had also been noted to sweat profusely and frequently to exhibit salt crystals on the skin. The mother volunteered that the baby "tasted salty" when kissed. On several occasions, after injections or when accidentally cut, the baby had demonstrated a bleeding tendency, which responded to the administration of vitamin K.

Three days prior to admission the baby had been seen in the pediatric outpatient department and placed on a normal infant diet. Subsequently he began to vomit at frequent intervals, more so in the few hours preceding admission; he became ill and his temperature rose to 104 F (40 C).

When brought to the hospital the patient was severely dehydrated, with markedly sunken eyes, depressed anterior fontanel, and poor tissue turgor. He was listless, crying weakly, and rolling his head slowly from side to side. There was an increased anteroposterior diameter of the chest, percussion of which gave a tympanitic note; no rales were heard on auscultation. Respirations were noted to be rapid and shallow. His body length was 67.5 cm. (26.5 in.), one standard deviation below the mean for his age. His weight, measured in the outpatient department three days earlier, was 5.8 kg. (12.8 lb.), more than three standard deviations below the mean for his age.

Serum electrolyte levels (table 2) determined at this time showed a markedly decreased chloride level, a moderately decreased sodium level, and a potassium level on the low side of normal. The pH was alkalotic. There was dramatic and rapid im-

TABLE 2.—*Serum Electrolyte Levels and Urine 17-Ketosteroid Values in Five Patients with Cystic Fibrosis of Pancreas*

Case No.	Date	Serum Electrolytes, mEq./Liter.						Urinary 17-Ketosteroids, Mg. per 24 Hr.
		Carbon Dioxide	Chloride	Sodium	Potassium	pH	Nonprotein Nitrogen	
1	1954							
	4-12, 2 p.m.	50	48	113	—	7.70	—	—
	4-12, 4 p.m.	44	56	119	3.0	7.35	79	—
	4-13, 9 a.m.	41	68	123	1.9	7.58	31	—
	4-14	34	95	139	2.9	7.60	—	—
	4-15	30	95	144	5.1	7.51	—	—
	4-17	30	100	140	5.5	—	—	—
2	1955							
	4-22	30	64	132	3.0	7.53	—	—
	4-23	24	87	130	2.9	—	—	—
	4-25	25	101	136	5.7	—	—	—
3*	1957							
	12-4, 3 p.m.	34	47	116	2.3	—	22	—
	12-5, 8 a.m.	21	106	139	4.7	—	—	—
	12-7	33	86	136	2.8	—	—	—
	12-9	25	96	133	4.3	—	—	—
	12-13	22	99	135	6.3	—	—	—
	1958							
	2-1	46	"too low to read"	114	—	—	—	—
	2-2	—	82	136	—	—	—	—
	2-3	31	80	137	2.3	—	—	—
	2-5	—	—	—	—	—	—	0.9
	2-6	38	80	140	3.4	—	—	1.2
	2-10	—	—	—	—	—	—	1.3
	2-11	—	—	—	—	—	—	0.6
	2-12	31	91	116	3.8	—	—	1.4
	2-17	—	—	—	—	—	—	1.2
4	1956							
	9-22†	—	100	120	5.5	—	—	—
	9-24	22	95	131	6.5	—	32	—
	9-25	23	105	136	4.9	—	—	1.1
	9-26	—	—	—	—	—	—	0.5
	9-27	—	—	—	—	—	—	0.5
5	1957							
	1-30†	—	—	127	—	—	—	—
	2-19	15	110	132	5.1	—	22	—
	2-21	19	110	137	5.0	—	24	—
	3-11	—	—	—	—	—	—	0.5
	3-15	—	—	—	—	—	—	0.6

* This patient had 2 hospital admissions.
† These determinations were made at other hospitals.

only 5 mEq. of sodium being excreted in the 24-hour urine sample on the fourth day of salt restriction.

Comment

With the exception of the patient in case 3, none of the patients included in this report was known to have cystic fibrosis before admission and this diagnosis was not even suspected. None of the four other infants (cases 1, 2, 4, and 5) had important pulmonary symptoms, nor, despite complete pancreatic insufficiency, was either the character of the stools or the abnormal appetite such as to attract attention.

The patient in case 1 was admitted in an emergency for treatment of extreme dehydration, and it was only after his recovery that the family history of fibrocystic disease led to further investigations which established the diagnosis. Because of the experience with this infant, when the patient in case 2 presented with a similar, albeit somewhat milder, picture the correct diagnosis was suspected. After this second experience it was realized that infants with cystic fibrosis are capable of developing hypoelectrolytemia even in cold weather, in response to stimuli other than heat. Accordingly, a sweat test was performed, after recovery, in all infants presenting the picture of hypoelectrolytemia not adequately explained by their symptoms. The behavior of the patient in case 3 was, therefore, well understood.

Cases 4 and 5 are somewhat different, because these patients were referred to us with the presumptive diagnosis of adrenal insufficiency and were seen only after the acute symptoms had been corrected. Here again, the knowledge that hypoelectrolytemia not adequately explained by the clinical symptoms may occur in patients with cystic fibrosis put us on the right track. A sweat test was performed and eventually the correct diagnosis was arrived at.

None of our patients suffered from diarrhea as a precipitating factor, and vomiting was moderate and insufficient, under normal circumstances, to explain the severe dehydration and electrolyte depletion. What, then, was the mechanism?

Greater than normal loss of electrolytes through sweating presumably occurred in these patients due to the abnormally high content of sodium chloride in their sweat. If the quantity of sweat they produced was excessive, this could not be ascribed to warm weather, since a number of the episodes occurred in midwinter. Diaphoresis may have been provoked by excessive covering of the body, which urban mothers are prone to inflict on their infants on the assumption that it wards off respiratory infections; concerning this aspect of the problem we lack satisfactory evidence in our own cases. Other illness, especially acute infections, may aggravate sweating. However, only one of our patients, the baby in case 1, was known to have symptoms of infection within two weeks prior to the recognition of hypoelectrolytemia; siblings of the patient in case 3 complained of abdominal pain and diarrhea shortly before the onset of the patient's illness, thus suggesting the possibility of a household infection of unidentified nature; but in the remaining three cases no evidence of prior infection was found.

Some factor other than excessive loss of electrolytes in sweat would appear to be involved. Study of table 2 would tend to substantiate this suspicion. The strikingly low serum chloride concentrations and the increased pH in the patients in cases 1 and 2 are suggestive of the metabolic alkalosis seen in patients who vomit excessively. In the patient in case 3 the blood pH was unfortunately not determined, but in other respects the serum electrolyte concentrations were similar to those of the patients in the first two cases. The amount of vomiting described would appear to be insufficient to cause these changes in a normal child, however, and one is led to wonder whether gastric secretions in a fibrocystic patient have higher sodium chloride content than average. This would certainly agree with the higher concentration of these electrolytes found in many other exocrine secretions in patients with this disorder, such as sweat, saliva, and tears.[3] Our attempts to determine the levels of sodium chloride and potassium in gastric secretions have been frustrated by technical difficulties.

Inspection of table 2 also reveals that electrolyte depletion must have occurred over a long period of time, for when the electrolyte loss is massive and rapid, as in the heat casualties of cystic fibrosis, only the extracellular fluid is affected; the serum potassium concentration remains normal and the level of sodium in the peripheral blood, even just before death, does not reach the low values which were found in cases 1, 2, and 3 of this report, despite the fact that much of the extracellular fluid volume has been lost.[1] In the present patients the intracellular fluid compartment was obviously involved as well, and the loss of electrolytes is presumed to have occurred slowly over a period of several days.

The adrenals in these patients can be exonerated on several counts. Conservation of sodium by the kidneys in three of the present patients was adequate in studies of dietary salt restriction (see figure). These investigations were not continued for longer periods because of the possible dangers of prolonged salt restriction in these infants. None of the three patients experienced clinical difficulty during the studies and none lost excessive amounts of weight. The serum electrolyte levels in the patient in case 5 appeared to be rather low at the end of the low-salt period but were similar to the ones preceding the experiment. This infant also happened to be the youngest of the three, a feature

On admission the patient appeared pale and semicomatose. His respirations were shallow and irregular. His skin was dry and its turgor poor. The eyes were sunken and there were petechiae on the abdomen.

A blood sample was immediately drawn for electrolyte analysis (table 2). Serum sodium concentration was low, serum chloride level "too low to be read," and carbon dioxide combining power elevated. Serum potassium level and pH were not measured on admission. It was felt that severe electrolyte depletion might have accounted for the convulsive seizure; in any event, the cerebrospinal fluid, examined the next day when the patient's condition had improved, was normal. The patient responded satisfactorily to fluid therapy, although his condition was critical for several hours after the start of treatment, and eventually his serum electrolyte levels approached normal values. Results of other laboratory tests were noncontributory. In particular, the excretion of 17-ketosteroids was within normal limits (table 2).

The patient was discharged, in satisfactory condition, after a two-week stay in the hospital and has done well since that time. His last visit to our outpatient department was on June 25, 1959, when he was 2½ years old, at which time his condition appeared good and his pulmonary involvement was under moderately satisfactory control with the continued use of antibiotics.

As shown in table 1, the fourth and fifth patients were admitted to Babies' Hospital for examination because of the suspicion of adrenal insufficiency.

Case 4.—A 6-week-old boy was transferred from another hospital on Sept. 25, 1956. His father and mother and four siblings were living and well. During the patient's first three weeks he had regurgitated on frequent occasions and had taken feedings poorly. Subsequently his appetite improved and he took his formula of evaporated milk well. However, he would vomit two or three times each day; after these episodes he was refed and he usually retained the second feeding.

Five days prior to admission to Babies' Hospital he was admitted to another hospital for investigation of the vomiting. Roentgenograms of the gastrointestinal tract and of the chest showed normal findings. The concentration of sodium in his serum was low and the serum potassium level was at the upper level of normal (table 2). It was felt that adrenal insufficiency was a possibility and the patient was transferred to our clinic for further study.

On admission the baby did not seem acutely ill. He weighed 3,050 Gm. (6 lb. 12 oz.), three standard deviations below the mean for his age, and was 46 cm. (18 in.) long, also three standard deviations below the mean. The chest was clear to auscultation and percussion. The genitalia were normal in size, and there was no excessive pigmentation.

Serum electrolyte concentrations were within normal limits at this time, as was the 17-ketosteroid excretion as determined in 24-hour urine collections on three separate days (table 2). After seven days the patient was discharged in good condition.

Two weeks later he was readmitted for duodenal drainage, which was attempted unsuccessfully. After the procedure his temperature rose to 103 F (39.4 C) and evidence of a pleural effusion developed. Hemolytic Staphylococcus aureus was grown from the purulent pleural material, and, despite intensive chemotherapy, the infant died 10 days after admission. Permission for autopsy was not obtained.

Case 5.—A boy was admitted on Feb. 18, 1957, at the age of 5 weeks, in good condition, having been referred from another hospital with the tentative diagnosis of "salt-losing syndrome." His father and mother were living and well. There was one sibling, now in good health, who had vomited at frequent intervals for the first three months of life.

After a normal delivery the baby began vomiting on the 2nd day of life and the vomiting had persisted until 12 days of age. A roentgenographic series of the upper gastrointestinal tract showed no abnormality at this time, but the baby appeared dehydrated. Chemical analysis on Jan. 30 (table 2), when he was 2 weeks old, revealed the serum sodium concentration to be low. He was then given intravenous fluid therapy, cortisone was administered for three days, and his serum electrolyte concentrations rose to normal values. The tendency to lose weight and become dehydrated was said to have persisted, although vomiting had disappeared.

On admission to Babies' Hospital the patient appeared chronically ill but was in no acute distress. His body length was 52 cm. (20.5 in.), two standard deviations below the mean for the age, and his weight was 3,380 Gm. (7 lb. 5 oz.), three standard deviations below the mean. His skin turgor was not good and there was marked loss of subcutaneous tissue. Physical examination otherwise was noncontributory.

Measurement of serum electrolytes at this time showed a slightly low serum sodium level (table 2), but the other laboratory examinations were noncontributory on admission. However, a roentgenogram of the chest showed the presence of generalized emphysema and relative microcardia, raising the possibility of cystic fibrosis. This diagnosis was substantiated by two sweat tests and by duodenal drainage for tryptic activity (table 1). Urinary excretion of 17-ketosteroids was found to be within normal limits in two 24-hour specimens (table 2).

On March 16, 1957, at the age of 2 months, the patient was placed on a formula of Lonalac, to provide a low-sodium intake for a period of four days. As shown in the figure, the conservation of sodium by the kidneys was satisfactory, a total of

From the practical, prophylactic standpoint, it is suggested that as soon as the diagnosis of cystic fibrosis is suspected in an infant, supplemental amounts of sodium chloride be added to the diet, even in cold weather. The additional amount administered orally should at least equal the infant's daily requirements and can be given in the formula. Special attention should be paid in such patients to the electrolyte balance when even minor degrees of vomiting develop.

Elevated concentrations of sodium and chloride were found in the breast milk of the mother of one of these patients, despite the fact she had been taking a low-salt diet for many years.

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LOCAL INJECTION THERAPY FOR RHEUMATIC DISEASES

A PRACTICAL GUIDE

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All types of rheumatic disease, defined in its broadest sense as including arthritis, periarthritis, myofibrositis, bursitis, tenosynovitis, and fasciitis, are considered by the authors to be amenable to treatment by the local injection of corticoid drugs. The authors use hydrocortisone but have not found evidence that it is superior to related compounds for this purpose. Both intra-articular and extra-articular injections have been found effective. The patient should be prepared for a painful phase after the effects of the locally given anesthetic have worn off, but if asepsis has been maintained there should be no complications. There have been no infections resulting from several thousand injections.

The busy physician needs a practical rapid reference as a guide in the use of local injection therapy for rheumatic conditions. Recent advances in the research on rheumatic diseases have produced such a prodigious library concerned with etiological, histopathological, biochemical, and therapeutic studies that even the professed specialist in rheumatology may have difficulty keeping abreast of the literature; the general practitioner or the physician in such an allied specialty as orthopedics may find the task utterly bewildering. The purpose of this paper, therefore, is to serve as a guide to the most widely accepted conclusions and to indicate reliable methods of treatment, avoiding conflicting or controversial data whenever possible.

Selection of Clinical Material

The term "rheumatic diseases" is defined here in its broadest sense with particular reference to arthritis, periarthritis, myofibrositis, bursitis, tenosynovitis, and fasciitis. All of these conditions were considered suitable for local injection therapy. Traumatic diseases were not placed in a separate category, since they were not basically germane to the subject material, except when certain phases of the traumatic lesions developed similarities to one of the major categories aforementioned.

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which may have a bearing on the situation. Additional factors ruling out malfunction of the adrenals are the low serum potassium levels during hypoelectrolytemia in the patients in cases 1, 2, and 3 (table 2), the normal values for urinary 17-ketosteroids in the patients in cases 3, 4, and 5 (table 2), and the lack of macrogenitosomia in these patients, which rules out adrenal hyperplasia with salt-losing syndrome, the commonest cause of adrenal insufficiency in this age group. Most important of all, these patients have been doing well since the occurrence of these episodes, in one instance (case 1) for as long as five years. This would have been improbable in the presence of adrenocortical insufficiency. In addition it has been shown that adrenal function is normal in patients with cystic fibrosis.[1]

I do not believe that patients with cystic fibrosis have any intrinsic lability of electrolyte balance or tend to become dehydrated easily. Observation of more than 600 patients, many of them severely ill or undergoing major surgical procedures (e. g., lobectomy, shunting operation for portal hypertension) without undue difficulty from electrolyte imbalance, is sufficient evidence on this score. It is only when additional factors are added, such as excessive loss of salt in sweating during heat or, as in the present cases, small but excessive losses over a period of several days or even weeks, that fibrocystic patients have salt depletion and dehydration.

In conclusion, infants with cystic fibrosis are apt to develop severe hypoelectrolytemia and dehydration even in cold weather. I believe this unusual susceptibility is explained by repeated small excessive losses through the sweat and possibly the gastric glands, which lead gradually to negative salt balance. Coupled with the known instability of water and electrolyte stores in infancy and the fact that the sodium chloride intake, in this age group, is frequently barely adequate to cover the usual requirements, this explains the clinical picture quite adequately. Furthermore, under these circumstances patients with cystic fibrosis are especially prone to develop sodium chloride deficiency of severe degree because of the abnormally high content of sodium cations and chloride anions in the secretions of their exocrine glands.[4]

Diagnostically it is important to realize that any infant in whom hypoelectrolytemia and dehydration are present or have occurred in the recent past, not adequately explained by severe vomiting or diarrhea, is to be suspected of having cystic fibrosis regardless of whether any other symptom of the disease is evident. A sweat test should be done in all these cases. It must be kept in mind that patients are frequently referred for study as possibly having adrenal cortical hypofunction (cf. cases 4 and 5, table 1) and that an infant less than 2 years of age has, in our experience, at least as much chance of having cystic fibrosis as he has of suffering from adrenal insufficiency as a basis for his symptoms.

From the practical, prophylactic standpoint, it is suggested that as soon as the diagnosis of cystic fibrosis is suspected in an infant, supplements of salt be added to the diet, even in cold weather. Unless the losses of sodium chloride are excessive, as through sweating, the additional amount administered orally should at least equal the infant's daily requirement of salt; the supplement can be given in the formula. Special attention should be paid in such patients to the electrolyte balance when even minor degrees of vomiting occur.

Finally, no comment should be attempted on the finding of high electrolyte concentrations in the breast milk of the mother of the patient in case 1, since these observations were made on only one subject. They are being reported to stimulate the interest of future investigators, with the hope that further observations will be made. It may be worthwhile to observe in passing that it is not outside the realm of possibility that, in a proportion of persons heterozygotic to the gene for cystic fibrosis, the sodium and chloride concentrations should be increased in breast milk, the secretory product of an exocrine gland. This would be quite in keeping with the finding of abnormally high sweat electrolyte values in some but not all relatives of known patients with this disorder.[5]

Summary

Patients with cystic fibrosis are known to be unusually susceptible to hot weather, because of massive salt depletion through the sweat glands. It is not generally appreciated that under certain circumstances infants with cystic fibrosis are prone to salt depletion and dehydration with serious consequences even in cold weather.

Five such cases are reported, in four of which the diagnosis of fibrocystic disease was not known or even suspected prior to admission.

On the bases of observation and of studies performed, it was concluded that in these patients renal and adrenal function were normal. The mechanism of salt depletion was thought to be repeated small excessive losses through the sweat and possibly in gastric secretions as well, coupled with inadequate oral intake, gradually leading to negative salt balance over a period of time. Under these circumstances patients with cystic fibrosis are especially apt to develop sodium chloride deficiency of severe degree because of the abnormally high electrolyte content of the secretions of their exocrine glands.

It is important to keep cystic fibrosis in mind in the differential diagnosis of hypoelectrolytemia and dehydration in infancy, especially when the clinical picture is not adequately explained by the amount of vomiting or diarrhea. Cystic fibrosis is at least as common as adrenal insufficiency as a cause of this symptom complex in this age group.

result of intra-articular injection of hydrocortisone acetate. The rapid rate of disappearance was taken as evidence that such decrease in concentration was not the result of simple diffusion across the synovial membrane.

Diagnostic Aids

The value of such laboratory aids as biopsy, blood count, sedimentation rate determination, and roentgenography is self-evident but not directly germane to this article. However, important practical information may be obtained from synovial fluid studies, the differential agglutination test (DAT), and the latex fixation test (LFT).

According to Ropes,[4] normal synovial fluid has the following characteristics: (1) a clear, pale yellow color; (2) an average count of about 60 cells per cubic centimeter (seldom up to 200), preponderantly mononuclear; (3) a viscosity of about 235 at 38 C; (4) mucin precipitates in tight clumps or strands in a clear solution when acetic acid is added to synovial fluid to make a 1% concentration of acid; (5) sugar concentration essentially the same as that of venous blood (fluid and blood should be drawn after six hours of fasting, allowing time for equilibrium before comparing their respective levels). Protein determination is seldom necessary as an aid in diagnosis. Routine cultures for bacteriological study should be made in suspected infectious arthritis.

When disease is present the synovial fluid shows the following significant changes: (1) turbid appearance and deeper color suggest inflammatory change; xanthochromia indicates bleeding within the joint antecedent to aspiration; (2) cell volume may rise to 3,000 per cubic centimeter in traumatic and degenerative arthritis; also in neurotrophic arthropathy; polymorphonuclear leukocytes appear and may rise to a maximum volume of 500 cells per cubic centimeter; (in rheumatoid and all forms of infectious arthritis the cell count is above 3,000 per cubic centimeter and the polymorphonuclear leukocyte volume is usually above 500); (3) viscosity is reduced significantly, down to an average of 14, depending on the severity of the inflammatory process; (4) mucin precipitates in softer, more friable clumps; surrounding fluid may be cloudy with flocculent or fibrous particles; (5) synovial fluid sugar level approximates that of blood in traumatic arthritis; sugar level is lowered and may be absent in chronic cases of rheumatoid arthritis; condition also obtains for infectious arthritis; reduction of fluid content of 30 mg. per cubic centimeter or more is significant; (6) protein volume averages 3.5 Gm. per 100 cc. in traumatic arthritis and exceeds 5 Gm. per 100 cc. in arthritis.

Differential Agglutination Test.—The differential agglutination test was developed by Rose and coworkers.[5] The principal reaction apparently occurs between an R factor in rheumatoid serum and a sensitizing gamma globulin coating the sheep cells, resulting in an agglutination of the sheep cells, probably an antigen-antibody reaction.

Latex Fixation Test.—Singer and Plotz[6] developed a latex fixation test based on the same principle as that used in the differential agglutination test. However, instead of using sensitized sheep cells, latex (polystyrene) particles of uniform diameter (0.8 μ) were substituted and suspended in a solution of pooled gamma globulin. The basic reaction seems to take place between some fraction of the pooled gamma globulin and the R factor in the patient's serum, resulting in an agglutination of the latex particles.

The latex fixation test has a specificity comparable to the differential agglutination test (70 to 72%). However, it has the advantage of easy storage of the reagent materials and the simplicity of requiring only a single dilution for the test.

Evaluation of Available Drugs

The first corticosteroid used successfully for injection of joints was hydrocortisone acetate. Subsequently, its use was extended to include other diseased areas of synovial and collagenous structure. Experimentation was then directed toward the perfection of a more effective drug which would not only produce a favorable local response but also would have the added virtue of prolonged activity. The drugs elaborated were analogs of hydrocortisone acetate. A form of phenylbutazone has been tried also.

Nomenclature.—Before entering into a discussion of the drugs specifically, it may be well to define and clarify their nomenclature, which is replete with synonyms, perhaps adding to the confusion of the general medical reader.

Cortisone is also known as cortisone acetate and compound E. Numerous proprietary names are given to this drug by the various pharmaceutical concerns, but the descriptive literature will designate the drug by its generic name or formula. Cortisone is now manufactured by chemical synthesis and is identified as 11-dehydro-17-hydroxycorticosterone-21-acetate. Its chief analog is prednisone.

Hydrocortisone is a derivative of cortisone used intra-articularly and locally. It is also known as hydrocortisone acetate, hydrocortone, hydrocortone acetate, compound F, and substance M. It is a synthesized adrenal cortical hormone and differs from cortisone only in the substitution of a hydroxyl (–OH) group for the ketonic (=O) group. It is identified as 17-hydroxycorticosterone-21-acetate. Its chief analogs are prednisolone and prednisolone tertiary butylacetate (prednisolone TBA). As with cortisone, hydrocortisone bears many proprietary names.

Experimental and Clinical Data.—The literature is now well documented with evidence of the efficacy of injectable corticosteroids in rheumatic joint and soft tissue diseases. There is general agree-

Arthritis.—All forms of arthritis were treated, except acute pyogenic and specific, such as tuberculosis. In general, cases of relatively short duration and lesser severity responded more satisfactorily than conditions of longer chronicity; osteoarthritis reacted more favorably than rheumatoid arthritis. Knees improved more readily than hips and ankles; shoulder and elbow response was usually good; and finger joints benefited only moderately.

Periarthritis.—Some confusion attends the definition of periarthritis, but ours is quite literal, namely, the involvement of structures intimately enveloping or associated with a joint, excluding the synovial (visceral) layer of the synovium. Fibrositis and capsulitis (adhesive bursitis or frozen shoulder) are examples. Ligamentitis, usually difficult to dissociate from a coexisting bursitis, falls into this category. Involvement of the medial collateral ligament of the knee and the underlying bursa is a good example of this lesion.

Myofibrositis.—Myofibrositis is not to be confused with the nebulous, more generalized form of fibrositis, which in most cases is a term of diagnostic frustration, applied to patients with maximal subjective complaints and minimal objective findings and probably representative of a psychosomatic syndrome. In our term of reference we are concerned with the more concrete physical manifestations such as specific localized muscle spasm, consistently elicitable trigger points of pain, and tender "nodules" palpable within muscle masses.

Bursitis.—Bursae are synovial-lined sacs, named and unnamed, which are placed functionally in areas of tissue friction. They act as lubricating "grease cups," being interposed wherever there is excursion of movable soft tissues over each other or over some nonyielding mass like bone. Thus, they may be found in any movable combination of tendon over tendon, bone, or ligament; or ligament over ligament or bone. Adventitious bursae develop when tissues are chronically subjected to pressure or friction of external origin. Local mechanical stresses, pathological changes in neighboring tissues, trauma, or infection may result in bursitis.

Tenosynovitis.—The tendon sheaths, like bursae, have a synovial lining and serve to facilitate frictionless excursion of the tendons which they surround. However, as the tendons function, they are frequently subjected to considerable stress, pressure, and friction. The ensuing inflammatory reaction involves the tendon sheath so that it may mechanically obstruct the gliding motion of the tendon. In chronic cases the sheath may become stenosed and adherent. In addition to the nonspecific mechanical irritations, bursae and tendon sheaths also may be directly involved by rheumatoid processes.

Fasciitis.—Static mechanical forces or nonspecific inflammatory changes may cause proliferation of fascial tissues. Plantar fasciitis and Dupuytren's contracture are classic examples of this syndrome.

Rationale of Local Injection Therapy

The principle of treating local rheumatic processes by local injection of drugs has merit if it helps to minimize the dangers inherent in systemic steroid administration. As we shall point out, the intra-articular injection of hydrocortisone produced local results which were comparable or superior to those obtained by the oral or parenteral routes.

The basic benefit from injection of hydrocortisone seems to derive from its antihyaluronidase action.[1] When hyaluronidase is liberated in tissue it produces an inflammatory reaction at the connective tissue level. This results in proliferation of fibroblasts, breakdown of ground substance, increase in capillary permeability, and edema. Administration of hydrocortisone apparently suppresses the hyaluronidase action and so prevents the undesirable features of inflammatory change.

In joints the basic effect of hydrocortisone also occurs at the connective tissue level. The intra-articular injection of hydrocortisone apparently alters the polysaccharide component hyaluronic acid and causes the abnormal pattern of synovial fluid to revert to normal characteristics. Response of the joint was manifested in the synovial fluid by an increase in the relative viscosity, a decrease in the number of nucleated cells, an increase in the concentration of polysaccharides, and an increase in the coagulability of the mucin clot formation. The return of the joint fluid characteristics to a more normal pattern was closely parallel to the improved clinical picture.

According to Wilson and colleagues,[2] when steroids were injected into a joint, the concentration of 17-hydroxycorticoids in the joint fluid decreased at the same rate for all preparations. The concentration was highest in the synovial cells after administration of hydrocortisone acetate and less with cortisone. Free-form hydrocortisone was found in the synovial fluid only, never within the cells. Another study showed that injected microcrystals of hydrocortisone disappeared from the synovial fluid within two hours and made their way into the synovial lining cells where they were retained. Hydrocortisone, being less soluble than cortisone in plasma, remained longer in the local area.

Wilson and colleagues [2] also reported that hydrocortisone disappeared rapidly from the synovial fluid: about 86% in the first hour and 97% after three hours. These figures were also substantially the same for cortisone, hydrocortisone acetate, and cortisone acetate. Clinical improvement was correlated with the rapidity of disappearance of hydrocortisone from the joint fluid.

Dal Cortivo and co-workers [3] observed no clinical improvement in a patient in whom a delayed rate of disappearance of hydrocortisone acetate from the synovial fluid was recorded. They presented evidence which indicated that changes in the chemical composition of synovial fluid took place as a

Number of Joints Injected.—As a rule, the more painful or acutely involved joints were in need of the relief offered by injection. Since multiple joints may be affected simultaneously in arthritis, it is permissible to inject several sites at one time. Weissmann-Netter and associates [13] recommended treating as many as 20 to 50 joints at one sitting, and they used general anesthesia in about one-third of their patients. They claimed to have given a total of 2 to 2.5 Gm. at one time without untoward effect. However, most observers agree that intra-articular therapy should be reserved for not more han two or three joints at a single treatment. We believe, along with most clinicians, that excessive multiple injections should be avoided.

Indications and Contraindications for Injection Therapy

Certain conclusions, evolved from the test of clinical trial, have been accepted as fundamentally ound in establishing the indications and contraindications for steroid injection in local therapy.

The suppressive action of hydrocortisone plays an mportant role in several situations. In rheumatoid rthritis, for example, locally active or more resistnt joints may be treated, pending benefits more lowly attained from systemic therapy by heavy metals or by orally or parenterally given cortisone. The suppression of inflammation may permit more ffective maintenance of systemic treatment or maintenance at a lower dosage level. Suppression f inflammation may be a necessary adjunct to mitation of deformity, use of physical therapy, and o preoperative and postoperative orthopedic surery. Finally, it may be the method of choice in ases in which systemic therapy is contraindicated.

Symptomatic relief through the injection of corcosteroids is valuable in such chronic conditions s bursitis, tenosynovitis, osteoarthritis, or gouty rthritis. It is frequently dramatic in its therapeutic elief of the acute phases of the aforementioned onditions.

The injectable hydroxysteroids are also effective gents in other extra-articular diseases such as Dupuytren's contracture, Heberden's nodes, the ainful soft tissue foci (trigger points) found in myofibrositis, and rheumatoid nodules of the skin nd subcutis.

The absolute contraindications for corticosteroid njection therapy are two: active infection in or ear a joint and sensitivity to hydrocortisone or the onstituent drugs incorporated into the suspending ehicle.

Relative contraindications include the following onditions, which have a clinically poor prognostic esponse to hydrocortisone: (1) active inflammation nvolving several or numerous joints; (2) disease of he spinal joints; (3) joints devoid of synovial lining; 4) failure to establish local improvement after multiple trials of injection; (5) severe acute traumatic derangement of a joint, with hemarthrosis; and (6) conditions whose diagnoses are not definitely established or are in doubt.

Injection Sites and Techniques in Intra-articular Disorders

The local injection of hydrocortisone may be considered under three headings: intra-articular, extra-articular, and special entities.

The intra-articular injections have techniques which are fairly well standardized. Generally speaking, one attempts to guide the needle into the joint space by the simplest anatomic approach, avoiding, if possible, pathways which harbor nerves and vessels. The introduction of the needle into the joint may be facilitated by careful passive movement of the joint. This excursion may aid the operator to "feel" the opening into the joint with the needle point. Diligent caution must be observed in avoidance of needle trauma to joint surfaces. Whenever the needle meets firm resistance, it should be withdrawn slightly and then advanced at a new angle. In most cases, especially in the larger joints, the needle meets no resistance if inserted accurately into the joint. A simple confirmation of joint penetration is obtained by injection of a small amount of air, which passes without resistance when the needle is within the joint space. As in any injection it is well to check needle penetration by aspiration to be sure that it is not within a blood vessel.

Temporomandibular Joint.—The temporomandibular joint is approached from the posterolateral aspect, well in front of the tragus of the ear, to avoid damage to the facial nerve. The direction of insertion is forward and slightly medial. Motion of the joint is a guiding factor in determining the needle's penetration into the joint space. The dosage is 25 mg.

Sternoclavicular Joint.—For injection of the sternoclavicular joint the patient is positioned supinely on the table, with the arm abducted 90 degrees from the side and dropping backwards over the edge of the table. This brings the clavicle forward and permits insertion of the needle from the medial aspect of the joint. The dosage is 25 to 35 mg.

Acromioclavicular Joint.—For injection of the acromioclavicular joint the patient is positioned supinely, with the arm adducted 15 to 20 degrees across the chest. This maneuver brings the medial aspect of the acromion into prominence. The needle is inserted at the superior aspect of the joint from the clavicular (medial) side and is pointed directly downward into the crevice of the joint. The dosage is 25 to 35 mg.

Shoulder Joint.—All approaches to the shoulder joint are subacromial. With the arm abducted 15 to 20 degrees the capsule is relaxed. Further "opening" of the joint space is obtained by an assistant making gentle downward traction on the arm; the patient may be sitting or supine.

ment by observers that when injectable steroids are used in the early stages of disease, improvement may be anticipated in 50 to 80% of the cases. The percentage was much higher in diseases of the knee, epicondylitis, and acute bursitis than in diseases of the hip, fibrositis, or chronic bursitis; likewise, response was higher in osteoarthritis and lasted longer than in rheumatoid arthritis. In one study of rheumatoid arthritis of the knees over a five-year period, 30% of the joints no longer required intra-articular injections, and an additional 50% were receiving continuing benefit from periodic injections. These figures compared, in osteoarthritis of the knees, with 60% complete relief and 15% continuing benefit from periodic injections.

Traumatic lesions showed a favorable response in 90% of the cases. However, we believe that these patients eventually would have made good recoveries as a natural resolution of the injuries and that injection of steroids did not hasten recovery; indeed, recovery may have proceeded in spite of the possible insult of steroid injection.

Choice of Drug.—Equally competent reporters were in disagreement about the comparative duration of effect of hydrocortisone TBA and prednisolone TBA. Norcross[7] found that hydrocortisone TBA was somewhat more effective than hydrocortisone acetate and approximately doubled the average duration of symptomatic relief in most patients; he found it inadequate, however, in some instances. Hollander and colleagues,[8] reviewing 171 patients, concluded that hydrocortisone TBA and hydrocortisone acetate were equally effective in 90% of patients but that the period of palliation from therapy with hydrocortisone TBA was greater in 60%, equal in 35%, and less in 5% of cases. He suggested that when the acetate is or becomes ineffective the TBA should be tried. Zuckner and co-workers[9] found no material benefit from giving hydrocortisone TBA over the acetate in 18 cases of rheumatoid arthritis and 20 cases of osteoarthritis. Gomes de Freitas[10] used trimethyl prednisolone acetate (Ultracortenol) in 40 cases and concluded that response was good in 30, fair in 5, and unimproved in 5 instances. He felt that the action was superior to hydrocortisone, as well as prednisolone, in effectiveness, but about equal to hydrocortisone acetate in duration of effects. Investigators were in general agreement that the use of procaine alone was markedly inferior to the combination of procaine and hydrocortisone.

Steinbrocker and Neustadt[11] tried injection of 20% solution of phenylbutazone at two-week intervals in 33 patients and claimed good results, especially in those with acutely swollen joints, improving the synovial fluid characteristics.

In our practice each of the major corticoids has been used. We have not been impressed by the superiority of one over another. At present our routine use of hydrocortisone acetate is quite satisfactory and without prejudice against the other analogs.

Dosage.—Some variance existed among investigators as to the concentration, dosage, and frequency of injection of drugs. Norcross,[7] dissatisfied with evidence indicating any outstanding superiority of one drug over another, decided to explore the possibilities of large doses. The knee joint was chosen because of simplicity of injection technique and because it offered a large internal synovial surface for absorption. Concentrations of hydrocortisone of 50 to 300 mg. per cubic centimeter were used; hydrocortisone TBA and prednisolone acetate, 25 to 50 mg. per cubic centimeter, were also used. Some solutions contained neomycin, 5 mg. per cubic centimeter, as an antibacterial agent. Eleven cases of osteoarthritis and 49 cases of rheumatoid arthritis were studied. Norcross[7] reported that marked relief, averaging 24 to 31 days, was obtained by administering hydrocortisone acetate in concentrations of 150, 250, and 300 mg. per cubic centimeter, as compared with only 6 to 11 days in lesser concentrations. Some of the patients disclosed systemic improvement, which included joints other than those injected. This was also reflected in increased urinary excretion of 17-hydroxycorticosterone-21-acetate. However, in some disagreement, others concluded that no more benefit was derived from injection of 100 mg. into the knee joint than was obtained from use of a smaller amount.

From a practical clinical standpoint we have decided independently that excessive doses (150 to 300 mg.) were not necessarily more effective than moderate doses (25 to 75 mg.), yet the moderate dose produced better responses of longer duration than the conventional smaller doses. It is obvious that smaller joints required injection of proportionately lesser doses. On the other hand, we think that a minimal effective dose for any site should not be less than 15 mg. The doses recommended for various areas will be considered individually under the treatment of the respective lesions.

Frequency of Injection.—One can only generalize on the frequency of injections, since the site of involvement, the acuteness or chronicity of the lesion, and the degree of response to the previous injections determine the need and time interval for reinjection. Bonner[12] recommended injections of 25 to 75 mg. at two-day intervals for four doses in treatment of acute subdeltoid bursitis. For the larger joints we recommend injections at 10-day to 20-day intervals, depending on how soon beneficial effects decline. If response is maintained, the injections may be postponed indefinitely; there is no need to repeat injections on an empirical basis. We found that joints did not benefit significantly from repeated injections at short intervals.

palpation, pressure over the center of the bursa in acute cases causes exquisite pain; a deflection of a few millimeters may produce only mild soreness. By the same token, hydrocortisone injected into the central area may yield rapid and dramatic relief of pain; injection into the periphery may give little or no beneficial response. The point of localization may be less specific in more chronic cases, since pain is not severe and the patient may be confused or uncertain about the exact location of pain. However, with painstaking repetition of palpation one can usually demarcate a small zone which is consistently more sensitive than the surrounding areas. The extra effort spent in determining this zone will be rewarded more frequently by clinical improvement after hydrocortisone injection than the haphazard injection on a hit-or-miss basis.

Routine Injection Technique.—The injection technique is initiated by formation of a small intradermal wheal with 1% procaine at the selected site of injection, with use of a 25-bore needle 0.5 in. long. By substitution of a 20-bore or 21-bore needle, 1.5 or 2 in. long, depending on depth of penetration necessary, procaine may be infiltrated slowly in a traight line directed at the projected bursal area. If diagnostic roentgenograms revealed the presence of calcium deposits in or near the bursa, an occasional uction pull on the plunger is indicated, in the hope of aspirating calcium. The recovery of calcium is atisfactory proof that an accurate injection is in progress. With the needle in situ one may flush and spirate, with about 2 cc. of 0.5% procaine solution. Most of this is recovered and the aspirated fluid which is more or less milky is discarded. The proedure is repeated until the procaine solution is eturned reasonably clear. At this point, with the needle still in situ, the prescribed dosage of hydrocortisone is injected.

Tennis Elbow.—"Tennis elbow" is an undifferntiated term to denote a radiohumeral bursitis, a ateral epicondylitis of the humerus, or a combinaion of the two conditions. With reference to injecion therapy the cardinal feature is the localization of tenderness over the head of the radius or over he prominence of the lateral epicondyle of the humerus. The routine injection technique is followed. The dosage is 25 to 50 mg. in either or both reas, as indicated.

Subdeltoid Bursitis or Supraspinatus Tendinitis.—he clue to the site of injection in subdeltoid buritis or supraspinatus tendinitis is the point of maximum tenderness elicited by palpation. If roentgenograms disclose the presence of calcium deposits, t is quite likely that in acute cases it will be possible o recover the calcium salts by irrigation-aspiration ith a single needle or by lavage through two eedles. At the end of this procedure, with the needle still in place, hydrocortisone is injected into he site of inflammation. The dosage is 50 to 75 mg.

Medial Epicondylitis.—Medial epicondylitis closely resembles lateral epicondylitis of the humerus, except that the muscle origins from the medial epicondyle are implicated. The routine injection technique is used. The dosage is 25 to 50 mg.

Bursitis of the Wrist.—Bursitis of the wrist is seen occasionally in relation to the ulnar collateral ligament and the pisiform bone. Roentgenograms may disclose calcific deposits. The routine injection technique is followed. The dosage is 25 to 35 mg.

Intermetacarpal Tendinitis.—Intermetacarpal tendinitis is an infrequent lesion which is seen usually as an acute condition with pain localized in one of the metacarpal interspaces, in relation to the head of a metacarpal, and occasionally along the shaft or at the base. Roentgenograms may reveal amorphous calcium. The routine injection technique is used. Unless the calcium deposit is unusually large, attempting its removal is unnecessary. The dosage is 25 to 35 mg.

Bursitis of the Greater Trochanter.—The greater trochanter has one of the larger bursae. Although local calcific deposits may be disclosed roentgenographically, their removal is not essential. The routine injection technique is followed. The dosage is 50 to 75 mg.

Bursitis of the Medial Collateral Ligament of the Knee.—Bursitis of the medial collateral ligament of the knee is indistinguishable from ligamentitis of the medial (tibial) collateral ligament. The routine injection technique is followed. The dosage is 35 to 50 mg.

Bursitis of the Lateral Collateral Ligament.—The involvement of the fibular collateral ligament is much less frequent than that of its tibial counterpart. Treatment is identical in both cases. The dosage is 35 to 50 mg.

Achilles Tendinitis (Bursitis).—In Achilles tendinitis or bursitis the involvement is at the insertion of the tendo achillis into the os calcis. The routine injection technique is used. The dosage is 25 to 35 mg.

Bunion Bursitis.—Hallux valgus deformity is not infrequently complicated by a bursitis overlying the medial aspect of the exostotic deformity. Periodic bouts of swelling, local inflammation, and pain follow the irritation of shoe pressure. Occasionally, a few drops of fluid may be aspirated from the bursal sac. The routine injection technique is followed. The dosage is 25 mg.

Subcalcaneal or Infracalcaneal Bursitis.—Subcalcaneal or infracalcaneal bursitis develops beneath the plantar surface of the os calcis, usually at the medial attachment of the plantar fascia. The presence of a calcaneal spur in the roentgenogram confirms the suspicion of a chronic irritating factor. The routine injection technique is used. The dosage is 25 to 50 mg.

The anterior approach is made medial to the head of the humerus; care should be taken to avoid the cephalic vein. The lateral approach is made over the greater tuberosity of the humerus, slipping beneath the tip of the acromion. The posterolateral approach is probably easiest where the acromion forms a wide shelf above the soft tissue depression of the posterior border of the deltoid muscle. The dosage is 50 to 75 mg.

Elbow Joint.—The approach of choice to the elbow joint is lateral. With the elbow extended about 135 degrees and the forearm midway between pronation and supination, the needle is inserted at the lateral aspect of the base of the olecranon process and directed medially and somewhat proximally. The dosage is 35 to 50 mg.

Wrist Joint.—With the wrist positioned passively in 20 to 30 degrees of extension the distal ledge of the radius is easily palpable on the dorsum. The needle is inserted just distal to the radius either at its midpoint or dorsolaterally, avoiding the extensor tendons. The dosage is 50 mg.

Metacarpophalangeal Joints.—For injection of a metacarpophalangeal joint the needle is inserted on either the medial or lateral side of the extensor tendon, slipping beneath the tendon into the joint space. Moderate traction on the finger may facilitate entrance into the joint by distraction. The dosage is 25 mg.

Interphalangeal Joints.—Technique and dosage are the same for interphalangeal joints as for the metacarpophalangeal joints, except that traction serves no purpose.

Hip Joint.—The lateral approach to the hip joint is favored by many, but we prefer the anterior approach for simplicity. The landmark is approximately over the head of the femur, at a point halfway between the anterior superior iliac spine and the latter tubercle of the pubis and 1 to 1.5 in. distal to the inguinal ligament. One should palpate for pulsation of the femoral artery to be certain the needle penetrates lateral to the vessel, checking by aspiration. A moderately rigid needle is preferable to a flexible one, since the latter tends to bend off course easily; a 4-in. 19-gauge needle is satisfactory.

The needle should be directed posteriorly and proximally until striking bony resistance of the neck, head, or acetabular rim. Then it should be withdrawn slightly and then, gently moving the hip alternately into flexion and extension by a few degrees, the needle should be permitted to "feel" its way into the joint. The hip is a difficult joint to enter, especially in patients with arthritis complicated by fibrosis and capsular adhesions. However, some benefit will usually accrue from the injection, even though the hydrocortisone is in juxta-articular or para-articular tissue. The dosage is 50 to 75 mg.

Knee Joint.—Some prefer the medial approach to the knee joint, opposite the midpoint of the medial margin of the patella. However, we believe that the lateral approach is preferable, entering opposite the midpoint of the medial border of the patella, directing the needle proximally to a 12 o'clock position. This approach permits the operator to work with freedom, eliminating the awkwardness of the medial approach which requires one to reach across the barrier of the other knee in the relatively small working space between the knees.

In ankylosis or flexion deformity of the knee, one may approach beneath either side (again we prefer the lateral) of the patellar tendon, through the infrapatellar fat pad into the joint space between the condyles of the femur. The dosage is 50 to 75 mg.

Ankle Joint.—The ankle joint may be entered anteromedially, just medial to the extensor hallucis longus, or anterolaterally, lateral to the extensor digitorum communis, medial to the fibular malleolus, and just proximal to the fatty areolar tissue of the sinus tarsi. The dosage is 25 to 50 mg.

Joints of the Foot.—No specific technique is suggested for injection of joints of the foot beyond the general principle of injecting at the point of maximum tenderness. Practically speaking, these are juxta-articular injections. The metacarpophalangeal or interphalangeal joints seldom require individual attention, but, when they do, the same technique is used as in the hand. The dosage is 25 to 50 mg.

Extra-articular Conditions Which Benefit from Injection of Hydrocortisone

The extra-articular conditions which benefit from hydrocortisone injection are considered herewith. In specific areas our routine injection technique is used. A description of this method follows the discussion of "bursitis."

Bicipital Tendinitis.—There is wide acceptance of the concept that tenosynovitis of the long head of the biceps brachii muscle is the most common antecedent of painful and stiff shoulders. It is characterized by an inflammatory process implicating the tendon–tendon sheath gliding mechanism of the long head of the biceps.

In treatment the needle is inserted at the point of maximum tenderness over the bicipital groove, avoiding the cephalic vein. Occasionally, in acute lesions, yellow or orange-tinged synovial fluid may be aspirated. With the needle in situ hydrocortisone is injected into the synovial sheath. The dosage is 50 to 75 mg.

Bursitis.—Most cases of bursitis have points in common diagnostically and therapeutically. For the sake of brevity and to avoid repetition these common factors may be grouped; individual variations will be noted under the specific headings. The single most important therapeutic factor is localization of the inflamed bursa, since efficacy of treatment depends largely on accuracy of injection into the site of the lesion. The almost infallible guide to localization in acute cases is point tenderness. It is amazing how circumscribed this point may be. On

Heberden's Nodes.—In the painful, acutely inflamed stage of Heberden's nodes relief from pain may be obtained by the action of locally injected hydrocortisone. A small amount of procaine solution is injected subcutaneously proximal to the node to obtain local anesthesia. This is preferable to direct injection into the node, since such an injection into the rather tense compact structure of the node would be painful. Subsequently, the hydrocortisone is injected directly into the node. If the tissues are unyielding the full dosage may not be injectable. The dosage is 15 mg.

Rheumatoid Nodules.—Rheumatoid nodules may have wide distribution in the skin and subcutis but are most frequently found over the olecranon and in the prepatellar soft tissues; occasionally they may become necrotic and ulcerate. Local administration of hydrocortisone, preceded by procaine, directly into the nodule may cause the nodule to melt away, thus avoiding the complications mentioned. The dosage varies according to the size and turgidity of the nodule. The dosage is 15 to 25 mg.

Surgical Conditions.—The use of hydrocortisone has been considered an adjunct to tendon surgery on the hypothesis that the drug would decrease the morbidity from adhesions. Experimentally, Gonzalez [17] showed that when the flexor tendons in dogs were bathed in hydrocortisone the functional result was no better than without use of hydrocortisone. He found no difference in the number or density of adhesions at the site of anastomoses. However, he stated that the tensile strength of the hydrocortisone-treated tendons was just as good as in the control subjects after three weeks. Finally, he raised a question about the undesirability of hydrocortisone remaining as a mass in the tissues.

Clinically, Howard and co-workers [1] gave the results of their observations. Hydrocortisone was used in six cases of tendons adherent after surgery; the condition of all six patients improved. Of four patients with flexor tendon suture, none improved after therapy with hydrocortisone. However, they concluded that after major reconstructive procedures hydrocortisone seemed to minimize the immediate postoperative reaction to surgery.

Complications

With the exception of injection of the knee joint and occasionally the shoulder and elbow joints, practically all injections of hydrocortisone for the treatment of intra-articular, extra-articular, and "special entity" conditions are attended by local reactions. After absorption of the locally infiltrated procaine, the pressure of the local collection of hydrocortisone in the zone of inflammation produces pain, varying from mild discomfort to acute distress. The reactive phase lasts usually from 4 to 8 hours, occasionally 24 to 36 hours. Psychologically, it is well to warn the patient to be prepared for a painful aftermath from injection. If he is fortified with analgesics before the effect of the procaine anesthesia wears off, and if he applies a cold compress to the area treated, his distress may be reduced and his morale preserved. After 24 hours, there is no objection to use of moderate heat locally for a maximum of one hour, three or four times daily.

With proper aseptic technique no infection should complicate injection. We have encountered no infection in several thousand injections. Hollander [18] reported four infections in more than 17,000 injections.

Finally, as a matter of speculative reflection, it is possible that the control of activity of the rheumatic process in joints treated by intra-articular administration of hydrocortisone may be associated with progression of the disease within other joints. On a hypothetical basis one could argue that improved knee function with control of pain, permitting continued use of weight-bearing joints, may lead to rapid progression of preexisting disease in the hips. In our opinion this objection is didactic, and even though some calculated risk may be involved, it should not militate against the greater over-all benefits that may accrue from injection of hydrocortisone.

Summary

Extensive clinical trial of hydrocortisone by local injection of patients with rheumatic conditions has established its value as a worthwhile therapeutic measure. While its indication may be equivocal in such conditions as surgical repair of tendons, Dupuytren's contracture, and the carpal tunnel syndrome, its high ratio of benefit is well confirmed in the more commonly encountered lesions of rheumatoid arthritis and osteoarthritis, the multiple manifestations of bursitis, fibrositis, tenosynovitis, and other allied conditions.

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"Special Entities" Benefiting from Injections of Hydrocortisone

Intra-articular and extra-articular injection techniques have been described. Finally, for the sake of completeness of subject matter, a group of special entities will be discussed.

Trigger Points.—Trigger points may occur anywhere in the musculofascial system, but, according to Sola and co-workers,[14] about 85% occur in four muscles: the trapezius, levator scapulae, infraspinatus, and scalenus. These authors studied 253 such lesions in 200 young adults. On palpation, sensitive areas may be localized within the soft muscles masses; in other cases "nodules" of firm consistency are palpable in contrast with the surrounding soft tissues. The routine injection technique is used. The dosage is 25 to 50 mg. in each area defined.

Stenosing Tenosynovitis.—In the hand the flexor tendon sheaths of the fingers and thumb are usually involved singly, but occasionally multiple involvement occurs. The site of predilection of sheath stenosis is over the palmar aspect of the metacarpal head. The tender area may be defined by palpation without difficulty. Localization is made easier if the patient is requested to slowly flex, then extend, the involved finger. This maneuver produces a break in the gliding action that may vary from a slight lag to a distinct jolt or snap as the tendon forces its way through the stenosed zone. This phenomenon has given origin to the term "snapping" or "trigger" finger. Occasionally, the finger or thumb will "lock" in the flexed (rarely in the extended) position, requiring passive manipulation to "unlock" the tendon.

For injection, a 23-bore needle 1.5 in. long is inserted slightly proximal to the point of tenderness and 1% procaine solution is infiltrated in the direction of the metacarpal head. On request, the patient gently flexes and extends the finger. The excursion of the tendon and its sheath at the stenosed band is noted easily and the operator attempts to engage this point with the needle's tip. Finger movement now produces a synchronous excursion of tendon, tendon sheath, and needle. The additional injection of procaine frequently will distend the sheath to its distal tip, but failure to produce ballooning of the sheath does not preclude a good result. Hydrocortisone is now injected. The dosage is 35 to 50 mg.

In the wrist, DeQuervain's disease is manifested as a stenosing tenosynovitis implicating the long abductor and short extensor muscles of the thumb as they glide in their grooves in the radial styloid process. The technique is essentially like the one described for the flexor tendons. The needle is inserted above (proximal to) the site of the lesion and directed distally beneath the ligamentous band which forms a roof over the involved tendon. The dosage is 35 to 50 mg.

In the leg, "shin splints" is also a form of tenosynovitis, usually involving the sheath of the tibialis anticus tendon. Active movement of the foot and ankle produces a palpable crepitation of the edematous tendon sheath that has been described variously as "banjo-string vibration," "starch crunching," or "snow-ball crunching." The injection of hydrocortisone locally is an effective adjunct to therapy. The dosage is 50 to 75 mg.

Carpal Tunnel Syndrome.—The carpal tunnel syndrome is characterized by inflammatory changes involving the tenosynovitic expansion within the tunnel, causing a compression of the median nerve with subsequent neuropathy. Kopell[15] reported favorable action due to reduction of the acute inflammation after injection of 25 mg. of hydrocortone in a 0.5-cc. solution at weekly intervals for three weeks. He stated that pain and paresthesia disappeared but that appearance and function were unchanged. We were not impressed with response in two of our patients, but one injection only of 25 mg. of hydrocortisone was given in each case. Perhaps multiple injections merit consideration. The dosage is as above.

Dupuytren's Contracture.—Hypertrophy and fibrosis of the palmar fascia, with secondary contracture in later stages, responded with "good results" according to Zachariae and Zachariae.[16] They treated 11 hands without performing surgery or giving other therapy. Weekly injections of hydrocortisone acetate for two to five weeks were especially effective in the new cases; a few severe cases failed to respond. If tenderness is present each of several areas may be injected. In the absence of pain the injection is given into one or more of the heavier fascial bands. The dosage is 25 mg. per area of tenderness.

Plantar Fibrosis.—Plantar fibrosis is an uncommon condition which is analogous to Dupuytren's contracture in the hand. The principles of treatment are identical.

Ganglion.—Mesothelum-lined cysts (ganglions) are usually synovial extensions from joint spaces or tendon sheath developing as hernial sacs. The protrusion of the ganglion with or without discomfort establishes the diagnosis, although in some areas, like the wrist, the ganglion may be deep rather than superficial. A skin wheal with use of procaine is the only anesthesia necessary, as a rule. Penetration of the ganglion is then made directly with an 18-gauge or 19-gauge needle to permit aspiration of the viscid, mucoid contents of the sac. In smaller sacs the needle containing mucoid material should be withdrawn completely after aspiration, to avoid reinjection of aspirated material still retained within the original aspirating needle, and a second entrance should be made into the bursa with a fresh needle for the injection of hydrocortisone. The dosage varies with the size of the ganglion. If the ganglion reforms, the aspiration and injection should be repeated before it enlarges unduly. If three injections are unsuccessful, surgery is indicated. The dosage of hydrocortisone is 25 to 75 mg.

more in some of the large limb muscles. The electromyograph can readily distinguish neuropathic diseases, or those affecting the lower motor neuron, from myopathic diseases, or those affecting the muscle fiber. Frequently it is important to distinguish those conditions affecting the axon primarily from those affecting the anterior horn cell. For example, poliomyelitis, progressive muscular atrophy (amyotrophic lateral sclerosis), and myelitis are various conditions affecting the anterior horn cell. Virus encephalomyelitis (Guillain-Barré syndrome), diabetic neuropathy, progressive neuropathic muscular atrophy (Charcot-Marie-Tooth disease), peripheral nerve injuries, localized neuropathy, and toxic neuropathy are among the many conditions which affect the axon primarily.

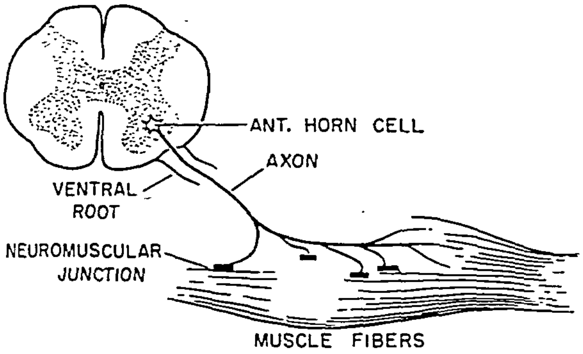

Fig. 1.—Diagrammatic representation of motor unit.

The differential diagnosis of these two groups of conditions is frequently quite difficult with the electromyograph alone. One way to distinguish between them would be to detect segments of altered excitability along the axon as a result of disease in this part of the lower motor neuron. This can be done by measuring the conduction velocity of the motor fiber, since it is usually reduced in conditions affecting the axon. Conduction velocity of normal human motor nerve varies from 40 to 70 meters per second. In newborn infants [1] the conduction velocity is 27 meters per second and, apparently, reaches adult values when the child is 2 to 5 years of age. The conduction velocity of motor nerves apparently is related to many factors, only some of which are known. The best-known factor is the diameter of the axon, the velocity varying in almost direct proportion to the diameter. Some other factors which affect the nerve conduction velocity are the temperature, age of the patient, local environment of the nerve, and degree of myelinization. Convenient peripheral nerves for this examination are the median and ulnar nerves in the forearm and the deep peroneal and posterior tibial nerves in the leg.

Review of Literature

Helmholtz, in 1852, with his relatively crude mechanical apparatus, measured the conduction velocity in the median nerve of human beings and found about the same results as are found with current apparatus. As more refined equipment was developed, more precise investigations of motor and sensory nerve conduction velocities were made by physiologists. Erlanger and Gasser,[2] in 1924, reported their classic study of motor and sensory nerves in the bullfrog and dog, demonstrating the relationship between conduction velocity and the diameter of the peripheral nerve and showing that the action potential of a mixed nerve resolves itself on the cathode ray oscilloscope into three or four spikes when the nerve is stimulated. Their conclusion was that the propagation rate varied in the various types of nerve fibers which comprised the nerve. In 1927, Erlanger [3] reported a study of the femoral nerve in warm-blooded animals and confirmed the hypothesis that the conduction velocity was almost directly proportional to the diameter of the nerve fiber. Hursh,[4] in 1939, reported a study of the relationship between the conduction velocity and the internodal distance. He also concluded that the conduction velocity was correlated with the diameter of the fiber. Gasser and Grundfest,[5] in 1939, reported a study which showed that the conduction velocity in the nerve fibers in cats and rabbits was almost directly proportional to the axon diameter.

In 1952, Wagman and Lesse [6] reported the relationship between the conduction velocity of motor fibers of the ulnar nerve and the age of the person (fig. 2). They found that the maximum conduction velocity of the ulnar nerve motor fibers is found in young adults and as early as the fourth or fifth year of life. In persons over 60 years of age, they found that the conduction velocity was reduced about 10% and discussed temperature alteration and metabolic and circulatory changes as explanations for this reduction. In 1952, Norris, Shock, and Wagman [7] reported the variations in the conduction

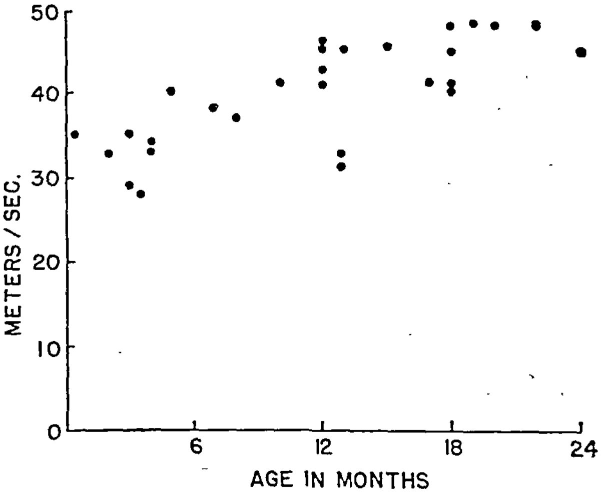

Fig. 2.—Relationship of age to conduction velocity of deep peroneal nerve in infants.

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CLINICAL VALUE OF MOTOR NERVE CONDUCTION VELOCITY DETERMINATION

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It is important to distinguish between neuropathic diseases that primarily affect the nerve axon and those affecting the anterior horn cell; for example, polyneuritis and poliomyelitis. Measuring the conduction velocity of the motor fiber, which is usually reduced in conditions affecting the axon is a practical electrodiagnostic procedure. The median and ulnar nerves in the forearm and the deep peroneal and posterior tibial nerves in the leg are suitable for such diagnostic study. Of 300 patients examined by this technique 41 had reduced velocity in one or more nerves. The diseases involved were virus encephalomyelitis, regenerating peripheral nerve injuries, progressive neuropathic muscular atrophy, chronic polyneuritis, and neuropathies due to diabetes, alcohol, or local lesions. The histories of a 6-month-old child with infectious neuronitis and a man with acute polyneuritis illustrate the use of this diagnostic procedure.

For more than a decade electromyography has been accepted as a diagnostic procedure in clinical medicine. Much newer to clinical medicine, but known for more than a hundred years to physiologists, is motor nerve conduction velocity determination. This examination provides important information to the electrodiagnostician, and it requires only a few minutes to complete. Because of its newness and its value in the differential diagnosis of diseases of the motor unit, we are presenting a report on a year's experience with this examination, which was given every patient referred to our electrodiagnostic laboratory for electromyography.

Background

The motor unit consists of the anterior horn cell, its axon, the neuromuscular junctions, and all the muscle fibers which the cell innervates (fig. 1). The number of muscle fibers per motor unit varies from a few, in the extrinsic eye muscles, up to 1,000 or

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phalanx of the fifth finger. Electrode jelly was used between all electrodes and the skin to provide satisfactory electrical contact. Frequently a small scratch was placed on the skin or the epidermis was sanded lightly to again reduce the resistance of the skin. The stimulating electrodes were placed over the ulnar nerve at the elbow with the cathode distally, and the intensity of stimulus was gradually increased until the muscle action potential viewed on the oscilloscope no longer increased in amplitude. At this point, the stimulus was increased 20 to 30% in intensity or, if the maximum voltage in the stimulator had already been reached, the duration of stimulus was increased. Then a photograph of the displayed electrical activity was taken. This procedure was repeated three times, and then the stimulating electrode was placed over the ulnar nerve at the wrist and the procedure repeated. The distance between points of stimulation at the elbow and the wrist was measured. The photograph was inspected and the conduction delay counted. Subtracting the delay at the wrist from the delay at the elbow gives the conduction time from elbow to wrist. The distance from the elbow to wrist in meters, divided by the conduction delay from the elbow to the wrist in seconds, gives the conduction velocity of the motor fibers of the ulnar nerve in meters per second.

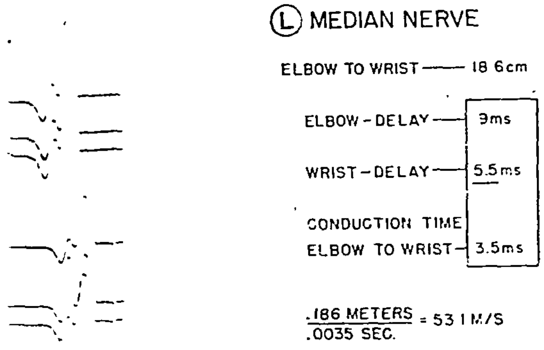

Fig. 4.—Example of record and subsequent calculation of determination of conduction velocity of motor fibers of median nerve. Conduction delay was counted to peak of response.

The median nerve is done in a similar manner with the pickup electrode over the thenar (fig. 4). In the leg, the deep peroneal is stimulated at the lateral aspect of the upper leg and at the ankle with the pickup electrode over the extensor digitorum brevis. The posterior tibial nerve is stimulated at the lateral aspect of the popliteal space at the knee and over the posterior aspect of the medial malleolus at the ankle with the pickup electrode over the belly of the abductor of the little toe. The average stimulus required 60 to 90 volts for 0.1 to 0.2 millisecond.

At the conclusion of the procedure the temperature in the vicinity of the motor nerve was taken with the needle thermistor. This is the most uncomfortable part of the procedure, since the needle is 1.5 in. in length and 22 gauge. The entire determination takes five to six minutes in a cooperative patient and causes relatively minor discomfort.

Table 1.—*Conditions in Which Motor Nerve Conduction Velocity is Reduced*

Condition	Patients, No.	Conduction Velocity (M. per Sec.)
Virus encephalomyelitis	12	1.8—34
Regenerating peripheral nerve injuries	10	10.8—37
Progressive neuropathic muscular atrophy	4	11.3—29
Diabetic neuropathy	6	29—38
Alcoholic neuropathy	2	30—36
Chronic polyneuritis	4	18—34.5
Localized neuropathy	3	28—25
Total	41	

* About 14% of patients examined.

Since the patient is usually in the supine position, the most convenient nerve in the leg to examine is the peroneal, and since the ulnar nerve in the arm is the most superficial and has the most easily identified landmarks, it is the one selected in the upper extremity. If diffuse disease was suspected, both nerves were examined. In infants and very small children, the posterior tibial nerve was much easier for us to stimulate. If local pathology along the course of the nerve was suspected, the nerve was stimulated both proximal and distal to the suspected lesion.

Comment

A total of 450 determinations were made on 300 patients during the year prior to this writing. Forty-one, or about 14%, had reduced velocity in one or more nerves after correction had been made for a reduction in temperature (table 1).

In the remaining 254 patients (table 2), the conduction velocity of the various nerves agreed substantially with those reported[14] in the literature. Our variation was slightly greater than others reported. However, there are several possible explanations for this. First, these determinations were made on patients in whom motor unit disease was suspected, not on normal persons. Second, the spread of ages varied from 2 to 77 years, with the largest

Table 2.—*Summary of Means and Standard Deviations of Conduction Velocities of Various Nerves in Normal Persons*

Nerve	Patients, No.	Conduction Velocity (M. per Sec.)
Peroneal	172	50.1±7.2
Median	68	53.0±6.4
Ulnar	67	55.1±6.4
Posterior tibial	20	50.2±9.3
Total	327	

velocity of the motor fibers of the human ulnar nerve in relation to the age of the patient. They were unable to explain the reduced velocity in older persons on the basis of selective degeneration of nerve fibers or of temperature changes. They suggested the possibility that alterations in membrane permeability or perhaps other characteristic changes of nerves cause this reduction in velocity.

Motor nerve stimulation with recording of the muscle action potential as a diagnostic aid in clinical medicine dates back to the early 40's when Harvey and Masland[8] made observations on patients with myasthenia gravis. They demonstrated that repeated stimulation resulted in a reduction of the muscle action potential in patients in this condition. Harvey and Kussler,[9] in 1944, reported the quantitative aspects of motor nerve function in patients with lesions of the peripheral nerve. They recorded the amplitude of the action potential when the ulnar, median, and peroneal nerves were stimulated. These same authors, with Tredway,[10] in 1945, reported the quantitative responses of stimulation of motor nerves in peripheral neuritis. They noted a reduction of the amplitudes when supramaximal stimuli were applied. Hodes, Larrabee, and German,[11] in 1948, reported the values of motor nerve conduction velocity in patients with peripheral nerve injury and hysterical paralysis. They paid particular attention to the amplitude of the muscle action potential as well as to the conduction velocity of the various nerves. They noted that the conduction velocity in peripheral nerve injuries was reduced during the phase of regeneration. They suggested that this reduction occurred because the diameter of the regenerating nerve was smaller than that of the original nerve and that the velocity, although it progressively increased during the first year after repair of the nerve injury, never regained more than 60% of normal conduction velocity. They also reported the response of the electromyogram to nerve stimulation, as well as the conduction velocity, as an objective record in hysterical paralysis.

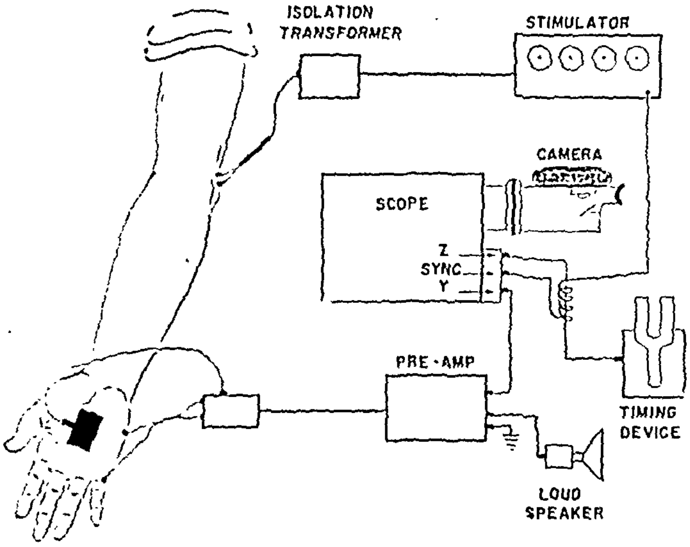

Fig. 3.—*Diagrammatic representation of conduction velocity apparatus.*

Hendriksen[12] reported, in a thesis, on the five-year study of nerve conduction velocities made at the Mayo Clinic by Lambert. The Mayo Clinic has been one of the few places in the country where this examination has been done routinely on patients referred for electromyography. Eaton and Lambert,[13] in 1957, reported the results of the electromyogram, both in response to patient activation of muscles and in response to supramaximal stimulation of nerves, in the diagnosis of diseases of the motor unit.

Instrumentation

Recently, commercially available accessories for electromyography, to make conduction velocity determinations, have been on the market. We have had experience with two of these and find they are at present less satisfactory than instruments assembled from separate components. The chief deficiencies are slow sweep speeds and inflexibility in changing the duration, intensity, frequency, and delay of the stimulus.

In our assembled components (fig. 3), a standard laboratory electronic stimulator provides short controlled pulses of unidirection current which is applied to a local segment of nerve for about 0.1 millisecond. The stimulator is isolated from ground by an isolation transformer. The stimulating electrodes are bipolar and have the cathode placed distally. The output of the stimulator triggered the sweep on an oscilloscope in such a way that the stimulus artifact was always photographed one millisecond after the tracing began. The pickup apparatus consists of two electroencephalographic skin electrodes. The active electrode is placed over the belly of the muscle, and the reference electrode is placed over its tendon. The action potential is picked up by the electrodes and amplified by a preamplifier whose output energizes an oscilloscope and an audio amplifier and loud-speaker. The electrical display, when photographed by a Polaroid Land Camera, permits quick examination of results and provides a permanent record of the examination. An accurate time base is provided by a 1,000-cycle-per-second tuning-fork oscillator applied at the Z axis of the oscilloscope so that the sweep is blanked out every millisecond. The oscillator is coupled to the stimulator so that the time base appears with each display. The intramuscular temperature in the vicinity of the nerve was taken by means of a needle thermistor connected to a bridge circuit.

Procedure

To determine the conduction velocity of the ulnar nerve, for example, the pickup electrode is placed over the abductor of the fifth finger and the reference electrode at the base of the proximal the sitting position. Electromyographic examination revealed diffuse lower motor neuron disease. The conduction velocity was 1.8 m. per second in the left common peroneal nerve and 5 m. per second in the left ulnar nerve. A diagnosis of infectious neuronitis was made. Since that time the child has been examined at bimonthly intervals, and the conduction velocity has now risen to 38 m. per second in the ulnar nerve and 35 m. per second in the left common peroneal nerve. The child was clinically well nine months after his admission.

CASE 2.—A 54-year-old man was admitted to University Hospital in December, 1958, with a diagnosis of probable amyotrophic lateral sclerosis. He had a two-month history of progressive diffuse weakness. Physical examination revealed evidence of recent weight loss, widespread fasciculations, and diffuse weakness in the distal groups of both his arms and [illegible] legs. Laboratory examinations showed normal results. Electromyographic examination showed diffuse lower motor neuron disease with the action potentials being reduced in number and increased minimally in amplitude and duration. The nerve conduction velocity was 24 m. per second in the ulnar nerve and 19 m. per second in the deep peroneal nerve. The diagnosis of acute polyneuritis was made and subsequent follow-up examination has confirmed that diagnosis.

Summary

The determination of motor nerve conduction velocity in the ulnar and median nerve in the forearm and posterior tibial and deep peroneal nerve in the leg is a convenient examination providing another use for electromyography. Its most valuable role is differentiating between those conditions which affect the axon primarily and those which affect the anterior horn cell. Pathological conditions affecting the axon usually alter the excitability along involved segments and, therefore, result in reduced conduction velocity.

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CALORIC CONTENT OF BEER.—For obvious reasons the diabetic patient must have his diet planned with sound knowledge and with accuracy. However, the features of palatability and satisfaction are particularly important to the diabetic because of the long periods that he must usually follow the prescribed patterns. Most clinicians prefer that the diabetic refrain from drinking any hard liquor, partly because such indulgence may lead to departure from almost all of his dietary restrictions. However, a glass or bottle of beer taken with food can not be expected to remove anyone's inhibitions. Moreover, the little alcohol contained in beer is not generally regarded as a carbohydrate, and it need not be counted as such in calculating the amount of carbohydrate supplied by the diet. For diet calculations it is sufficient to assume that an eight ounce glass of beer supplies 9.4 gm of carbohydrate, 0.8 gm of protein, and 104 calories.—C. E. Dutchess, M.D., Malt Beverages. *Industrial Medicine and Surgery*, December, 1959.

proportion in the range 2 to 10 years. Next, we occasionally measured to the peak of the action potential rather than to the take-off when the latter was not definite. This represents an average difference of 4 m. per second. Finally, several different physicians performed the examinations.

We did not include in the calculations of normal the children under the age of 2 years. This was because the conduction velocity of newborn children averages 27 m. per second and, in our series, approached normal by the age of 18 months to 2 years (table 2).

The temperature of the extremity is important in the determination of conduction velocity since, frequently, the temperature of a paretic extremity may be 2, 3, or even 4 C (3.6 to 7.2 F) below the normal temperature of the extremity. The temperature in the leg was cooler than that in the arm. This might explain the higher values in the ulnar and median nerves. The average temperature in the leg was 33.5 C (92.3 F), and the average temperature in the forearm was 35 C (95 F). Hendriksen[12] found that the conduction velocity was reduced 2.4 m. per second for each drop in degree centigrade. One of us (K. J. O.) has data which suggest that the conduction velocity is reduced 5% per degree centigrade. The importance of recognizing the relationship of temperature and conduction velocity necessitates taking the intramuscular temperature with each abnormal determination. We have had occasion to measure the conduction velocity in children 3 and 4 years old who had a temperature of 104 F (40 C), and, at this temperature, we have recorded conduction velocities as high as 81 m. per second, and the temperature of an extremity may be in excess of 37 C (98.6 F). The reduction in the nerve conduction velocity is present in diabetic neuropathy and can be quite helpful in making a diagnosis, especially when similar symptoms can be caused by circulatory insufficiency.

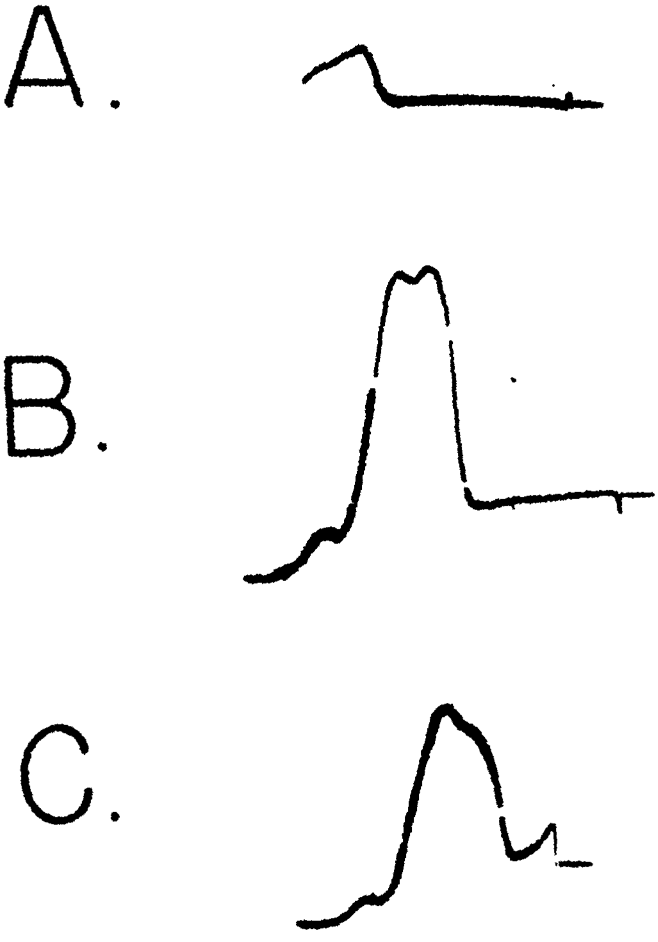

Fig. 5.—Record of stimulation of ulnar nerve above the elbow (*A*), below elbow (*B*), and at wrist (*C*). Increase in delay and reduced muscle action potential when ulnar nerve was stimulated above elbow suggests local neuronopathy of ulnar nerve at elbow.

Frequently localized pathology along a nerve can be identified and localized with the use of supramaximal stimuli and nerve conduction velocity. Such local lesions occur in the carpal tunnel syndrome with the median nerve at the wrist and with tardy ulnar nerve palsy in the ulnar nerve at the elbow. Stimulating proximal to localized neuropathy will give prolonged conduction time as well as reduced amplitude of muscle action potential (fig. 5). Then, stimulating distal to the lesion, the nerve conduction velocity will be normal, as will the muscle action potential. The conduction delay in median nerve at wrist in carpal tunnel syndrome is increased beyond the normal 4.5 milliseconds.[15]

Frequently it is difficult to differentiate virus encephalomyelitis from poliomyelitis. However, measuring the nerve conduction velocity provides a very useful objective method for making this differential diagnosis, since the conduction velocity is normal in poliomyelitis and reduced in virus encephalomyelitis. It may not be reduced until several weeks after the acute phase, but we have found a reduction as early as one week after the onset of the disease. In the very young and uncooperative child, motor nerve stimulation studies are of great value since they do not require the cooperation of the patient.

Report of Cases

Case 1.—A 6-month-old boy was referred to Children's Hospital in October, 1958, with a diagnosis of probable muscular dystrophy. He had had an insidious onset of progressive weakness without systemic symptoms. Muscle biopsy specimens had been taken at another hospital and a diagnosis of myopathic disease was made. On physical examination, he had flabby, soft muscles and hypermobility of the joints. There was diffuse weakness and none of the muscles of the extremities worked against gravity. His head dropped when he was pulled to

Classification of Syndromes

Syndromes naturally vary, usually according to the number and localization of cysts in the brain. A number of classifications have been proposed. Stepien and Chorobski,[5] from 23 cases of their own and a review of 71 surgically treated patients reported in the literature, suggested three categories.

Group 1.—The first group consists of persons with signs and symptoms common to expanding intracranial tumors. Of the 94 surgically treated patients, 67% fall into this group. The cerebral hemispheres were involved in 60.3%, the posterior fossa in 14 patients (the fourth ventricle in 11), the fourth ventricle and base of the brain in 2, and the cerebellopontine angle in 1. The chiasmal-hypothalamic region was occasionally involved. Cysticerci within the fourth ventricle are usually solitary and are easily removed. This is the type most amenable to surgical correction.

Group 2.—The second group includes seven patients. The principal findings are those of diffuse cerebral swelling, increased intracranial pressure, papilledema, pleocytosis and elevated protein values in the cerebrospinal fluid, and mental changes. There are multiple widespread cysts (more than 200 have been counted in a single brain). The prognosis is very poor, and operation can offer only temporary palliation through wide decompression.

Group 3.—Twenty-four patients are placed in group 3. The cysticerci are located mainly at the base of the brain, where they provoke a proliferative inflammatory reaction in the basilar meninges. Internal hydrocephalus results, manifested by headache, nausea, and vomiting. Occasionally there is cranial nerve paresis. Mental disturbances are less common and less pronounced than in group 2. Operation offers only temporary benefit.

Diagnosis

Cysticercosis cerebri should be considered among the uncommon conditions capable of imitating brain tumor, particularly in patients who have lived in countries where the disease is prevalent. Preoperative diagnosis is usually impossible, except when calcification of cysts is roentgenographically demonstrable in muscle or brain. Calcification occurs more slowly and less frequently in the brain than in the muscles. In their review of 284 cases, Dixon and Hargreaves [10] found only 32 patients with cerebral calcification, and in only two instances was calcification apparent in the skull roentgenograms.

There are no pathognomonic changes in the cerebrospinal fluid or peripheral blood. Eosinophilia is an exceptional finding. Lymphocytic pleocytosis and elevated protein values in the spinal fluid are uncommon. A spinal fluid complement-fixation reaction is accurate in about 60% of cases. The test should be performed whenever cysticercosis is suspected and a specific antigen is available.

The diagnosis may be verified by biopsy when subcutaneous cysts are palpable, or when calcified cysts are shown in roentgenographic films of muscles. The cysticercus of T. solium is easily distinguished from the larger cysts of T. echinococcus. It contains a single invaginated scolex which has four suckers and a double row of hooklets. The only tapeworm larva that may cause confusion is that of Multiceps multiceps. Human infestation results from accidental ingestion of dog feces. In its larval stage M. multiceps forms not a cysticercus but a coenurus. Intracranial coenuri are usually large (3 cm. or more in diameter), and each coenurus contains multiple scolices.

Treatment

The only treatment is surgical intervention, and its value is now established. Best results are obtained in patients with a solitary cyst in an accessible area of the brain or ventricle.

Stepien and Chorobski [5] considered over-all results good in 50% of 94 surgically treated patients. In patients in group 1, whose signs and symptoms resembled those of brain tumor, recovery or improvement occurred in 72.6%. In group 2 and group 3, the benefit patients obtained from operation was brief and palliative.

Report of a Case

A 45-year-old man awakened from sleep on July 11, 1951, with bilateral pounding headache, nausea and vomiting, and a temperature of 103 F (39.4 C). He had been a professional baseball player most of his adult life. For the past 10 years he had been a scout for a baseball team. He was born in Texas and had lived all his life in North America, except for two trips of several weeks' duration (as a baseball scout) to Mexico.

Rest and antibiotics were prescribed, with a presumptive diagnosis of viral meningitis. During the next few weeks his condition improved considerably. On Sept. 14, 1951, he sustained a severe sunburn at the beach, after which nausea and vomiting recurred for two days and the headache again became severe. He also complained of pain and limited motion of the left shoulder. Roentgenograms showed calcified tendinitis of the rotator cuff. Mainly because of the shoulder pain he consented to hospitalization at the Glendale Sanitarium and Hospital on Sept. 17, 1951. Physical examination showed retinal hemorrhages, papilledema, and vertical and lateral nystagmus. The hemogram was normal. Chest x-ray was normal. Skull films were ". . . negative for evidence of bony or intracranial change." An electroencephalogram was read as "mild, bilateral temporal-parietal-occipital dysrhythmia, without consistent tendency to lateralization." With x-ray therapy the shoulder pain rapidly improved, and the patient insisted on leaving the hospital on Sept. 19, 1951.

CYSTICERCOSIS CEREBRI

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and
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A 45-year-old man suddenly experienced headache, nausea, vomiting, and fever with findings leading to a presumptive diagnosis of meningitis. His course thereafter was one of temporary recoveries and recurrences, with repeated manifestations of high intracranial pressure. The diagnosis of intracranial tumor seemed likely. Ultimately a suboccipital craniotomy made it possible to remove from the fourth ventricle a free-floating cyst in which a cysticercus cellulosae was identified. Ataxia and diplopia persisted after the operation. About two years later headache and other symptoms of intracranial pressure reappeared, and the patient died suddenly two and one-half years after the operation. The essential pathological changes found at autopsy were limited to the brain and meninges.

That certain worms, particularly the larval form of the pork tapeworm, can "worm" their way into the human brain, has been known for many years. In the United States, however, infection of the brain with cysticerci of Taenia solium is rare and is not often considered in the differential diagnosis of a patient with signs and symptoms of an expanding intracranial lesion.

Until recently there was no effective treatment for cysticercosis cerebri. Dandy,[1] as recently as 1938, concluded that "surgical treatment is of no avail." This view has been revised during the past decade, and the value of neurosurgical intervention is now established. Results are often favorable, occasionally curative; in any case, operation offers the only hope for survival.

Since 1957 five cases of cysticercosis cerebri have been reported from the United States. Of the three cases reported by White and co-authors,[2] two represented solitary cysts, and surgical results in the patients were favorable; in the third patient, epileptic fits due to multiple calcified cysts in both hemispheres were controlled with anticonvulsant drugs and no operation was indicated. Dent's[3] patient died a few weeks after the first operation. The patient whose history we record made a good recovery after operation but died two and one-half years later.

History and Epidemiology

Panarolus[4] in 1650 first described cerebral cysticercosis in a man who died in a fit. Excellent recent summaries of the problem have been published by Dixon and Smithers[4] and by Stepien and Chorobski.[5]

In Poland there was a remarkably increased incidence of cerebral cysticercosis in the decade after 1936, which Stepien and Chorobski[5] attribute to poor wartime hygiene. Bickerstaff and co-authors[6] pointed out that the increasing frequency of the disease in England was probably due to the large numbers of persons returning from the East. Cysticercosis of the brain is prevalent in Mexico, Spain, parts of Central and South America, Eastern Europe, and the Far East. Robles[7] found that in Mexico of 100 cases of expanding intracranial growths, 25 were due to T. solium cysts. In China, Yen-Fang and co-authors[8] detected cysticercosis cellulosae in 30.8% of 26 postmortem cases of Japanese B encephalitis. They believe that preexistence of cerebral cysticercosis predisposes to Japanese B encephalitis, with an increase in mortality.

The pork tapeworm is found wherever raw or inadequately cooked pork is eaten, or where sanitation standards are poor. With troops returning from abroad, and with an influx of immigrants from countries where the disease is prevalent, it is likely that more cases will be seen in North America.

Man is the only known definitive host of the adult tapeworm (T. solium). He acquires the infection by eating inadequately cooked pork which contains encysted larvae.

Man may also serve as the intermediate host—by fecal contamination of food, or possibly by autoinfection through regurgitation of ova. This condition is called cysticercosis and is the form of the disease we are discussing here. When an ovum hatches, it liberates an oncosphere which penetrates the intestinal wall and enters the blood stream. Thus, embryos may be distributed throughout the body. Within 60 to 70 days an embryo develops into the larval form (cysticercosis cellulosae). Cysticerci may be found in many tissues, but the most frequent site for encystment is the brain. Arana Iniquez and Asenjo[9] report intracranial cysts in 40 to 82% of cases of human cysticercosis.

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diagnosis was "posterior fossa tumor." Even at this point none of us considered the possibility of cysticercosis cerebri. We should have done so.

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CONSERVATIVE MANAGEMENT OF "LOW BACK SYNDROME"

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The effectiveness of a new muscle relaxant, carisoprodol, was tested in a study of 212 patients with pain, immobility, and muscle spasm in the lower part of the back. Conservative treatment, which included analgesic drugs and physical therapy, was used in a contratest group of 106 patients; the test group of 106 other patients received the conservative treatment plus carisoprodol. The initial dosage of carisoprodol was generally one 400-mg. tablet four times daily. The patients treated with carisoprodol returned to work in about one-quarter the time it took the conventionally treated patients. An equally striking difference was observed in a smaller study in which a contratest group of 35 patients received placebos. Six case histories illustrate the types of situation in which a relaxant drug can be expected to relieve the "low back syndrome."

Disorders of the lower part of the back are a constant problem to orthopedic surgeons. While rupture of an intervertebral disk is one of the common causes, the term "low back syndrome" is really a name for a variety of conditions characterized by pain, immobility, and muscle spasm of the lower part of the back. The spasm is a reflex phenomenon, due to irritation of the nerves, which sets up a vicious cycle of pain, spasm, more pain, and so on.

A logical part of therapy is to break this vicious cycle. If the muscle spasm can be relieved by any method, relief of pain and the restitution of normal movement will follow, in most instances. There are a number of methods for accomplishing this, such as bed rest, with or without traction, to eliminate nerve compression; infiltration of the painful area with procaine hydrochloride or other local anesthetics; and manipulation. These methods may actually reduce a partially herniated disk; in general, however, their aim is to relieve muscle spasm for a prolonged symptom-free period. Such conservative treatment is adequate for complete recovery in most patients.

A medicament which can be taken orally, has prompt and prolonged action, and can relieve muscular spasm and pain will have obvious value in such a program. For this reason I tried carisoprodol (Soma) (N-isopropyl-2-methyl-2-propyl-1, 3 propanediol dicarbamate), a new compound of the propanediol series, which had been found to be a central muscle relaxant when tested in animals. Pharmacological studies also showed that in rats the drug relieved pain due to experimentally pro-

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He was readmitted to the hospital on Sept. 28, 1951, complaining of stiff neck and frontal and occipital headache. Examination showed bilateral retinal flame hemorrhages, bilateral papilledema (2 D.), 2+ neck rigidity, and no pathological reflexes although the deep tendon reflexes were sluggish. Lumbar puncture showed an initial pressure of 340 mm. H_2O, and the fluid contained 30 monocytes and 43 polymorphonuclear leukocytes per cubic millimeter. The total protein level was 0.062 Gm. per 100 cc., chloride level 440 mg. per 100 cc., and blood sugar level 32 mg. per 100 cc. Repeated lumbar punctures revealed persistent elevation of pressure, and the leukocyte count varied from 20 to 100 per cubic millimeter, with no eosinophils. Smears and cultures of the spinal fluid were negative.

The hemogram was normal (eosinophils 3%). Results of the Mazzini flocculation and the heterophil-agglutination tests were negative, as were complement-fixation tests for equine encephalomyelitis. Repeated electroencephalograms showed mild cerebral dysrythmia, with tendency to lateralize in the left posterior hemisphere. Findings of stool examinations and cultures were negative.

The patient became afebrile, and after each lumbar puncture was clinically remarkably better. Nevertheless, evidences of intracranial pressure persisted, and a ventriculogram was performed on Oct. 19, 1951. The lateral and third ventricles were distended but showed no lateral shift. On none of the views did the fourth ventricle fill, although the first portion of the aquaeductus cerebri (aqueduct of Sylvius) was seen. This suggested a lesion in the region of the fourth ventricle, producing obstruction and internal hydrocephalus. Suboccipital craniotomy revealed a free-floating cystic mass in the fourth ventricle, without apparent attachments, which was nearly 2 cm. in diameter. To be sure that there were no other cysts in the fourth ventricle, the vermis cerebelli was split in the midline, allowing better exposure. A catheter was inserted into the third ventricle, and this proved to be open.

The pathologist's report was as follows: "The specimen consists of a previously emptied, white, thin walled, smooth lined cyst, 1.6 by 1.4 cm. in size. Sections of the structure show a cysticercus cellulosae. The sections passing through the apparent scolex show tubular openings representing the suckers, and a central space with serrated lining, probably representing the rostellum and its hooklets. Diagnosis: Cysticercus cellulosae of the brain (fourth ventricle)."

The patient made a good postoperative recovery. By Oct. 29, 1951, his appetite was normal, he had neither pain nor headache, and he enjoyed being outdoors in a wheelchair. However, he complained of ataxia and diplopia. He was discharged on Nov. 4, 1951.

At home he was quite well and moderately active for nearly two years, although ataxia and diplopia persisted. Late in 1953 headache and other symptoms of intracranial pressure recurred, but he refused to return to the hospital for further investigation. He suddenly died at home on March 1, 1954.

Autopsy was performed on the embalmed body on March 2, 1954. Examination of the brain after fixation in formalin disclosed dense adhesions between the dura mater, including the tentorium, and the midline portions of the cerebellum posteriorly. The arachnoid membrane over the lateral surfaces of both hemispheres was moderately thickened and clouded, especially along the tufts of the major sulci. In both parietal regions the residua of old trephinations of the skull were found, and on the right there was slight herniation of the brain through the trephination. At the base of the brain the arachnoid membrane over the chiasmal and basilar cisterns was considerably thickened. There was moderate dilatation of the lateral ventricles, more on the right than on the left. Necrotic lesions were found adjacent to the lateral ventricles in the left parietal and in the right occipital regions. Sections through the brain stem and cerebellum disclosed thickening of the ependyma of the aquaeductus cerebri and the fourth ventricle. The cerebellar vermis had undergone considerable secondary necrosis adjacent to the surgical incision.

Examination of the cardiovascular system, respiratory system, peritoneum and digestive system, hepatic system, spleen and lymphatic system, urinary system, genital system, endocrine system, and musculoskeletal system revealed no gross abnormalities.

Microscopic examination of the brain showed arachnoidal thickening and inflammatory reaction. There was severe perivascular round-cell infiltration, foreign body reaction, and cerebellar necrosis. The pituitary gland was compressed, and the pars posterior was distorted by an arachnoidal reaction of granulation and hyperplasia. There was evidence of congestion and hemorrhagic edema of the lungs; the kidneys also showed congestion. No lesions were demonstrated in the pancreas, skeletal muscles, heart, spleen, gallbladder, adrenals, liver, or thyroid.

Anatomic diagnoses were (1) cysticercus cellulosae of brain (fourth ventricle), surgically removed; (2) arachnoiditis, adhesive, chronic; and (3) cerebellar vermis necrosis, secondary.

Summary

A 48-year-old man died of cystercosis cerebri. He survived surgical removal of a solitary cyst in the fourth ventricle for two and one-half years.

Preoperatively the diagnosis had been in serious doubt although, after the patient's hospital stay and performance of multiple tests, the consensus was "intracranial neoplasm." After ventriculography the manipulation was used on patients while they were taking the drug, this procedure was greatly facilitated by the relaxation and relief of pain they had obtained.

The most significant difference between the two groups was in the time required for recovery. The table shows this for the 91 patients who recovered in the shortest time in both series. Because in the group treated with carisoprodol there were only 91 patients who returned to their usual occupation after strictly conservative treatment (due to the fact that 6 had to be operated on and that treatment was changed in 9 patients), the average time they required to recover was compared with that of the 91 in the group treated by conventional methods who returned to work in the shortest time. Even on the basis of this calculation, the patients treated with carisoprodol returned to work in about one-quarter of the time it took the conventionally treated patients. The average figures for the two groups, according to this calculation, were 11.5 and 41 days, respectively; if the average time for all the conventionally treated patients had been taken, the proportion would have favored carisoprodol treatment even more. Thus, treatment with carisoprodol saved the patients who recovered on conservative treatment alone (and this constituted the vast majority) an average of about one month of abstinence from their regular activities.

No serious side-effects were noted from therapy with carisoprodol. Although blood cell counts and urine examinations were taken routinely and other tests performed as seemed indicated, no abnormalities which could be attributed to the drug were observed. Mild side-effects consisted of drowsiness in nine patients, skin rash in two, pruritus in two, and nausea in one. Since the skin rashes and pruritus disappeared even though therapy with the drug was continued, it is not likely that they were drug reactions. The drowsiness was relieved in all but one instance by diminishing the dose of the drug; treatment of one patient, who developed both drowsiness and nausea, was discontinued, although it is not certain that this was necessary. No tendency for the patients to increase the dose of medication themselves or to develop a tolerance to it was noted, nor were withdrawal symptoms observed when administration of the drug was stopped.

Six illustrative cases are given below.

Report of Cases

Case 1.—A 46-year-old man was bending down in his apartment to pick up a paper from the floor when he felt a severe pain in the right lumbar region. He was not able to straighten up and had to be carried into his bedroom, where he stayed in bed for two days before he was brought to my office. Examination revealed that his pelvis was inclined and that he had complete rigidity in the lower lumbar region, with elimination of the lumbar lordosis. Since his trunk motions were completely restricted, he had great difficulty in moving about. The results of routine clinical tests were found to be significant for nerve root irritation. Roentgenography revealed incomplete sacralization of the transverse process of the fifth lumbar vertebra on the right side, with narrowing of the interspace of the disk space above. A complete blood cell count and the erythrocyte sedimentation rate were within normal limits.

Comparison of Results of Treatment of Low Back Syndrome with Carisoprodol and by Conventional Methods

	Therapy			
	Carisoprodol		Conventional	
	No.	%	No.	%
Total patients	106	...	106	...
Total episodes of low back syndrome	106	...	117	...
Age, Yr.				
Range	17-79	...	21-71	...
Average	41.3	...	44.8	...
Sex				
Male	63	...	67	...
Female	43	...	39	...
Type of low back syndrome				
Acute	62	...	84	...
Recurrent	41	...	29	...
Chronic	3	...	4	...
Dosage, mg. per day				
900	2	...	...	...
1,200	20	...	...	...
1,600	83	...	...	...
3,200	1	...	...	...
Average	1,528		...	...
Duration of carisoprodol therapy, days				
Range	2-22	...	...	...
Average	10.8	...	...	...
Response rate				
Excellent	23	...	13	...
Good	61	...	27	...
Total	84	79	40	34
Fair	11	...	34	...
Poor	11	...	43	...
Total	22	21	77	66
Time required for recovery in 91 briefest cases, days				
Range	2-21	...	3-90	...
Average	11.5	...	41	...
Reasons for changing therapy				
Surgery (operation performed)	6	...	7	...
None (hospitalized or treatment changed because of inadequate response)	8	...	17	...
Side-effects (nausea)	1	...	...	...
Total	15	14	24	22

The patient was advised to rest at home, mostly in bed on a firm mattress. Since he weighed 182 lb. (82.7 kg.) and was 6 ft. 2 in. (188 cm.) tall, two tablets of carisoprodol were given him three times daily and an additional two tablets before bedtime.

Four days after administration of the drug the patient came to the office, where it was found that the list of the pelvis had disappeared and there was hardly any spasm. The patient felt subjectively well and had the following trunk motions: He could bend forward without pain to an angle of 40 degrees and could place his fingertips 12 in. from the duced joint irritation and that it appeared to suppress central perception of pain without abolishing reflex defense withdrawal reactions.[1]

Method of Study

One hundred six consecutive patients with the low back syndrome, treated with carisoprodol, were studied. These were compared with another 106 consecutive patients with 117 episodes of the low back syndrome who had been previously treated by conventional methods without the use of muscle relaxant drugs. (A pilot study, in which placebos and carisoprodol were used by the alternate case method, was made at the beginning of the investigation. In all, 35 patients were given placebos. However, the difference between the active drug and the placebo was so obvious that it was believed a placebo study should not be made on private patients.)

All patients were seen in my private practice of orthopedic surgery. All were evaluated by the usual complete orthopedic examination as well as by roentgenograms of the spine, blood cell count, erythrocyte sedimentation rate, urinalysis, and appropriate blood chemistry studies. Patients with conditions such as malignant tumors, osteoarthritis, and doubtful cases of disease were excluded from the study.

Initial treatment was always conservative. All patients stayed at home at the beginning, usually in bed, supported by a bed board or a firm mattress. The patients were cautioned against sudden stooping, twisting, or lifting; heat was applied to the affected area, and analgesics were given as needed. Manipulation was performed and physical therapy used in those patients in whom it seemed indicated.

Carisoprodol was administered as an adjunct to this conservative therapy. The initial dosage for most of the patients was one tablet (400 mg.) given four times daily, after meals and at bedtime. Small patients were given less. The dosage regimen was continued until satisfactory relief of pain and muscle spasm was obtained, and then diminished. If only partial relief of symptoms was obtained, medication was continued at its initial level. The drug was never given for more than 14 days unless some response was obtained. The patients treated with carisoprodol were, therefore, given the same conventional treatment of the low back syndrome as I had used previously, except for the addition of the drug.

Evaluation of the results was based on the patients' subjective opinion concerning pain and their ability to get about and on the physician's objective evaluation of posture, muscle spasm, localized tenderness, and limitation of mobility. In general, improvement was noted in all signs and symptoms simultaneously.

Evaluation was recorded on the basis of two criteria: First and most interesting was the response rate, or rate of recovery. Although this is what interests both patient and physician, it is a gradual process depending on judgment and impossible to measure exactly. The response rate was therefore judged to be excellent, good, fair, or poor, depending on the time it took for the patient's condition to improve significantly. An excellent response was defined as one in which there was marked (50% or more) relief of signs and symptoms within four days or less. A good response was defined as one with marked improvement within 7 days and a fair response as one with marked improvement in 14 days. Responses were considered poor if there was no significant relief within 14 days, if there was any side-effect of an untoward nature, or if so little relief was obtained that the patient had to be hospitalized or some other treatment had to be instituted.

The second criterion for evaluation was the time required for recovery, defined as the time in days when the patient could return to work or whatever had been his or her ordinary occupation. This definition has the advantage of being started as a definite number but does not indicate how soon the patient began to get relief.

Results

A summarized comparison of the results from both series is shown in the table. More detailed statistics on the 106 patients treated with carisoprodol and on the 106 patients treated by conventional methods showed that the patients in the two series are comparable with regard to age, sex, and the type of low back syndrome which they presented.

The rate of response was excellent or good in 79% of the treated group but in only 34% of the group treated by conventional methods alone. As expected, some of the patients given conventional treatment did well, but the differences between the two groups were clinically striking as well as statistically significant ($p < 0.01$). The initial effect of carisoprodol on muscle spasm was sometimes noted in a few hours, and usually by the third day, even in patients who did not have a marked response until several days later.

There was significant relief of pain from the use of carisoprodol. This was usually associated with relief of muscle spasm but was often noted by the patient before muscular relaxation could be demonstrated. Improved ability to get about, improved posture, diminution of localized tenderness, and increased motion as demonstrated by objective measurement were all noted in the patients who had relief of pain. This is not surprising in view of the pain-spasm cycle noted above.

In patients with whom physical therapy was used, carisoprodol produced relaxation during such therapy and seemed to prolong its effect. When were almost completely obliterated. Results of all the cardinal manipulative tests were 3+ to 4+ positive.

The patient weighed 164 lb. (74.5 kg.) and was 5 ft. 9.5 in. (177 cm.) tall. One tablet of carisoprodol was given three times daily and at bedtime for five days. On the third day he returned and stated that he felt a greater improvement than he had experienced in the past when other types of therapy had been administered. Continuing the use of the drug, the patient was completely relieved of symptoms by the ninth day.

Comment

Positive myelographic findings were demonstrated in 17 patients in the group treated with carisoprodol. Fortunately, all obtained some relief from use of the drug, so that operation was performed on only six patients. This is about the same number as those who required operation after having had conventional treatment. Carisoprodol was helpful, however, to the patients who needed operation, both preoperatively and in the postoperative period, even though it was not adequate to give complete relief. It is interesting that a few patients who required an operation had obtained such improvement from treatment with carisoprodol that their response had to be classified as good, even though they did not get complete relief until after operation.

Other drugs, such as aspirin, codeine, and meperidine hydrochloride were given, as indicated, for pain. In most instances these were not needed after therapy with carisoprodol had been started or could be given in minimal dosage.

Eight of the 106 patients in the group given carisoprodol showed no benefit from the drug. They are listed as "none" in the "time required for recovery" column of the table, because administration of carisoprodol was discontinued and they were either hospitalized to receive traction or put on therapy with another drug. It should be noted that, if this same criterion of failure were applied to the group given conventional treatment, 17 patients would be included. Thus, 21% of the patients given conventional treatment required an operation or were hospitalized, compared to the 14% of patients who required an operation or had their treatment changed while receiving carisoprodol.

Summary and Conclusions

One hundred six consecutive patients, seen in a private practice of orthopedic surgery for the "low back syndrome," were treated conservatively, with carisoprodol (Soma) (N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate) given as adjunctive therapy.

The results obtained in these patients, compared to those obtained in a similar group who had been given only conventional conservative therapy, are as follows: 1. The usual dose of carisoprodol for adults was one tablet (400 mg.), taken with meals and at bedtime. 2. Use of the drug significantly speeded up the rate of recovery and greatly shortened the time required to return these patients to work. In the group treated with carisoprodol, 79% experienced complete or marked improvement in seven days compared to 34% in the conventionally treated group. 3. The effects of carisoprodol were shown by relief of pain and relief of localized muscle spasm, so that the patients showed improvement in their ability to move about and assume a normal posture earlier than patients in the group treated by conventional methods. The effects of the drug also facilitated the use of physical therapy and orthopedic manipulation of the back, as well as giving comfort to the patient and diminishing the need for administration of analgesic drugs. 4. Operation was necessary in only 6 of the 106 patients treated with carisoprodol, and in 7 of the 106 patients treated by conventional methods alone. 5. No serious undesirable effects were noted to result from administration of carisoprodol, even when it was given for several weeks.

Conservative management is the method of choice for the "low back syndrome." By means of this, operation may be avoided in many instances, even when a herniated intervertebral disk has been proved to be the cause. Conservative management, however, often is slow, attended by discomfort, and may include hospitalization and traction.

The use of carisoprodol seems to be a valuable adjunct to the care of the patient with the "low back syndrome." With use of the drug, the time patients required to return to work was shortened to about one quarter of the time needed in a comparable group of patients treated by conventional methods. Particularly gratifying was the drug's ability to relax muscular spasm, relieve pain, and restore normal movement. In addition, its use facilitated manipulation, which also speeded recovery in a number of patients. Its prompt action, ability to provide objective and subjective assistance, and freedom from undesirable effects recommend it for use as a muscle relaxant and analgesic drug of great benefit in the conservative management of the "low back syndrome."

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The carisoprodol used in this study was supplied as Soma by Wallace Laboratories, New Brunswick, N. J.

NOTE: More detailed statistics comparing patients treated with carisoprodol with those receiving conventional treatment can be obtained from the author.

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floor. Results of the manipulative tests were 1+ to 2+. He also could move around, leave the house, and resume some of his activities. He could not, however, return to work at that time.

He continued to take the two tablets three times a day, with an extra two tablets before bedtime; three days later this patient was practically free from all his symptoms. No other treatment was included in the management of this patient, neither analgesic medication nor physical therapy, and he returned to work on the ninth day.

Case 2.—A 19-year-old female patient was in an automobile accident. She developed severe pain and spasm in the lumbar spine, with radiation into both buttocks. She had great difficulty in walking but was able to come to my office. Her medical history was noncontributory. She was 5 ft. 9 in. (175.6 cm.) tall and slender. Lumbar lordosis was diminished and her pelvis was level. Trunk motions were completely eliminated. Results of all manipulative tests were 4+, with both buttocks and thighs symmetrically involved. Roentgenograms revealed changes in the lumbosacral spine consistent with a so-called unstable fifth lumbar vertebra. The lumbar lordosis was reversed. Complete bed rest was prescribed and 300 mg. of carisoprodol was given three times daily, for 5 days; thereafter the dosage was reduced to 200 mg. three times daily, for 4 days. Her response was slow, with about 50% improvement of the symptoms and objective findings on the sixth day. On the seventh day there was more marked improvement. In 14 days the patient was free from her subjective and objective symptoms. Her progress was followed for seven and one-half months and proceeded without relapse.

Case 3.—A 51-year-old man was seen at home with an acute left-sided sciatic syndrome. An attorney by occupation, he had never experienced any trauma. His medical history was completely negative for incidents of lumbago, backache, or automobile accident. The onset of illness was sudden, and the patient was unable to get around. Examination revealed considerable muscular spasm in the lumbar region, with trunk motions 75% eliminated. Results of all manipulative tests were 4+. Neurological changes were not present; findings of urinalysis were normal. Complete bed rest was ordered, and 400 mg. of carisoprodol was given with meals and at bedtime for three days, followed by a half-dose for six days. On the second day there was 25% improvement of the symptoms; four days later there was little spasm, and results of trunk motion and manipulative tests were only 1+ positive. On the 10th day after onset the patient had very mild, residual subjective complaints. There were only minor objective findings: 1+ on the left for the Lasegue test, and mildly positive on the left side for the Nachlas test. Roentgenograms taken at this time revealed moderately advanced degenerative disk changes of L-4 and L-5. This patient's progress was followed for six months, and he has had no recurrence of his illness.

Case 4.—A 49-year-old man had been seen by various physicians on and off for 18 years. Highly neurotic, he was not given the benefit of doubt by any consultant, including myself. Eighteen years after the onset of symptoms, the attacks of lower back syndrome with right sciatic radiation became so frequent that an exploration was carried out, without myelogram. A massive disk hernia was removed at the right lumbosacral interspace, and a spinal fusion was performed. The patient's postoperative course was uneventful, and he went back to work eight weeks postoperatively, against advice. In the 10th postoperative week he suffered an acute recurrence, with complete obliteration of trunk motions. Roentgenograms taken at that time were not remarkable. It was assumed that the patient had either bleeding or a possible infection. Results of all the tests performed were normal. He was put to bed and given 400 mg. of carisoprodol with meals and at bedtime, for four days. He was symptom-free in four days, without residual objective findings when manipulative tests were performed. The patient's progress is being followed, and, at the time of writing, 11 months have elapsed since the operation.

Case 5.—A 44-year-old female patient with recurrent lower back syndrome had been treated for four years. Roentgenograms revealed lumbosacral instability, with the fifth lumbar vertebra 2 mm. posterior to the sacrum. Previously she had received protracted courses of physical therapy. She was hospitalized twice, in 1953 and again in 1955, with bilateral Bucks' extension. In August, 1958, she developed another attack. Her lumbosacral motions were completely eliminated. Results of all manipulative tests were 4+. She was given 400 mg. of carisoprodol with meals and at bedtime for 10 days. On the third day after the onset of symptoms the patient received also physical therapy, such as application of heat by means of a hydrocollator, sinusoidal stimulation, and active exercises. It was interesting to observe that this attack was shorter than any she had had previously. Her condition improved considerably in 10 days, and she recovered in 17 days. Further attacks are to be expected.

Case 6.—A 38-year-old male laborer was suffering from a recurrent disk syndrome due to congenital anomalies in the lumbosacral junction. He had previously been treated by many methods, and usually it took several weeks of physical therapy and rest, with administration of codeine, aspirin, and meperidine hydrochloride and, on one occasion, two weeks' treatment by traction in a hospital, to eliminate his symptoms. With this fourth recurrence, the patient's pelvis was tilted, his lumbar lordosis was reversed, and his trunk motions

Although the subcommittee recognizes that chloramphenicol is a valuable antibiotic, it is also the opinion of the subcommittee that there is no longer a reasonable doubt that chloramphenicol may cause aplastic anemia. Periodic blood cell counts may be of some help; however, they cannot be relied on to detect signs of marrow toxicity sufficiently early so that chloramphenicol administration can be discontinued before an irreversible aplastic anemia develops. Therefore, judicious use of the drug must be the rule, and it should not be used prophylactically, in trivial infections, or in infections in which other, less dangerous antibiotics may be used effectively.

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COUNCIL ON FOODS AND NUTRITION

Report to the Council

The following six papers were presented at the symposium on "Nutritional Problems in Medicine" in Nashville, Tenn., May 8, 1959. This symposium was sponsored by the Council on Foods and Nutrition and Vanderbilt University Medical School.

PHILIP L. WHITE, SC.D., *Secretary.*

Introduction

This is the sixth symposium on nutrition sponsored jointly by the Council on Foods and Nutrition of the American Medical Association and a medical school of the United States. These symposiums are designed to summarize for the physician and other medical scientists current progress on nutritional subjects of timely interest to medicine. The following collection of papers on nutritional problems in medicine is presented to illustrate the intimate role of nutrition in medicine—a role better recognized by the great ancients in medicine than by some of our moderns. For example, Celsus wrote, "After having spoken of those things which benefit by depleting, we come to those which nourish, namely food and drink. Now these are of general assistance not only in diseases of all kinds but in preserving health as well; and an acquaintance with the properties of all is of importance, in the first place that those in health may know how to make use of them, then, as we follow on to the treatment of disease, we can state the species of aliments to be consumed. . . ."And Hippocrates wrote, "For the art of Medicine would not have been invented at first, nor would it have been made a subject of investigation (for there would be no need of it), if when men are indisposed, the same food and other articles of regimen which they eat and drink when in good health were proper for them, and if no others were preferable to these. . . ."

The following discussions focus on some aspects of nutrition in heart disease and in defects of absorption as illustrations of the empirical wisdom of the ancients modified by the science of the present.

This is the second symposium which it has been the privilege of Vanderbilt University School of Medicine to co-sponsor. We are grateful for this opportunity and appreciate the participation of the speakers and visitors, the assistance of the staff of the Council on Foods and Nutrition, and the help of many who have made this program possible. I wish especially to acknowledge the role of Dr. George V. Mann in the organization and planning of this symposium.

WILLIAM J. DARBY, M.D., Ph.D.,
Director of the Division of Nutrition
Vanderbilt University School of Medicine
Nashville, Tenn.

J.A.M.A., April 30, 1960

COUNCIL ON DRUGS

Report to the Council

The Council has authorized publication of the following report.

H. D. Kautz, M.D., *Secretary.*

The Registry on Blood Dyscrasias sponsored by the Subcommittee on Blood Dyscrasias of the Committee on Research has received a number of case reports concerning the possible association of a blood dyscrasia with the use of chloramphenicol. The subcommittee has concluded that it might be proper to caution the profession by publishing a reminder concerning the potential ill-effect of this drug on the hematopoietic system. It is hoped that publication of this information will render a service to the medical profession.

Norman De Nosaquo, M.D., *Secretary,*
Committee on Research.

BLOOD DYSCRASIAS ASSOCIATED WITH CHLORAMPHENICOL (CHLOROMYCETIN) THERAPY

With an increase in the receipt of reports by the Registry on Blood Dyscrasias in which chloramphenicol is associated with the development of a blood dyscrasia, it becomes important once more to review briefly the toxic effect of this drug on the blood-forming organs of sensitive persons. The paucity of recent publications in the American literature should not be construed to mean that the reports of chloramphenicol-induced aplastic anemia some years ago were merely a chance association. There have been numerous reports in more recent years of chloramphenicol-induced aplastic anemia in the foreign literature.[1] Between January, 1953, and January, 1960, the Registry on Blood Dyscrasias has received a total of 223 reports of pancytopenia; of these, 91 were cases in which chloramphenicol had been administered. Of the 91 cases, there were 34 instances in which chloramphenicol was reported as being the only drug given.

Severe reactions to antibiotics occurring in patients between late 1955 and early 1957 have recently been studied in a nationwide survey by Welch and colleagues[2] of the Food and Drug Administration, Department of Health, Education, and Welfare. This study reported on 31 patients with aplastic anemia associated with chloramphenicol administration, of whom 23 died. Of these 31 cases, only 8 had been reported to the registry. Although some of these patients may have received chloramphenicol in the presence of a developing aplastic anemia, this explanation seems improbable. It is important to note that, in the survey of the FDA, few cases of aplastic anemia were associated with the administration of penicillin, streptomycin, the tetracyclines, or a sulfonamide.

The Subcommittee on Blood Dyscrasias recognizes that chloramphenicol is a valuable and important addition to a physician's armamentarium. This is particularly true since it has been shown that certain strains of staphylococci resistant to penicillin and the tetracyclines are sensitive to chloramphenicol. The manufacturer has repeatedly directed the attention of the medical profession to the need for judicious use of the drug by a warning statement in the labeling and advertising of the product. Although the warning statement specifically cautions against the indiscriminate use of the drug or against its use for minor infections, an examination of the reports received by the registry reveals that the drug has been used in such conditions as upper respiratory infections, including the common cold, bronchial infections, asthma, sore throat, and tonsillitis, miscellaneous urinary tract and ear infections, undiagnosed low-grade fever and even disseminated lupus erythematosus, gout eczema, malaise, and iron deficiency anemia. It is incumbent upon a physician when he prescribes chloramphenicol that he carefully weigh the need for the drug in relation to the risk of possible serious toxic effects.

water, but the ratio of the two is unbalanced, and the intercompartmental segregation becomes abnormal. Thus, although sodium retention is the primary difficulty and water retention is secondary in the formation of edema, we must take into account that in some stages of the disease there is an accompanying misregulation of the mechanisms governing water intake (thirst) as well as water excretion.

Whenever we give a drug which primarily increases excretion of one or another cation or anion, we assume that the kidney will balance the excretion of other substances in order to keep the body composition normal. Sometimes, however, the kidney may not do this, indicating that it has lost its selective function and that the stimuli to the kidney are not operating in proper concert.

Regulation of water and various electrolytes is accomplished by highly selective and separate mechanisms and manipulation of electrolyte excretion may not be followed by favorable adjustment of water excretion. Some clinical features of the edematous patient with congestive cardiac failure may be related to what is called in other circumstances "water intoxication."

Edema is managed by causing a diuresis which produces a negative sodium and water balance. The diuresis mechanism should leave the patient with a normal body composition. Diuresis or negative balance of water and sodium by methods which derange body composition is undesirable, since it accentuates some electrolyte abnormalities while correcting others. A common example is the action of some diuretic drugs in causing further potassium depletion in patients with cardiac failure while removing the excess sodium and water.

Diuresis may stimulate the mechanisms causing potassium loss in three ways: First, the diuretic drug (such as mercury, ammonium chloride, carbonic anhydrase inhibitor, or chlorothiazide) may increase potassium excretion by its direct effect on the renal tubule cell exchange of ions. Second, sodium and water loss with contraction of body fluid volumes may stimulate further those mechanisms (particularly the excretion of aldosterone) which are acting on the kidney to retain the sodium and enlarge body fluid volumes. Third, the potassium loss may cause myocardial weakness and potentiate digitalis toxicity, which in turn will further stimulate the renal mechanisms to retain sodium and lose potassium. This is a vicious circle.

The best way to heal misregulation of electrolytes due to cardiac failure is to improve or alleviate the cardiac failure. Electrolyte abnormalities of cardiac failure are completely reversible only if the patient's cardiac failure is reversed. This demands careful and thorough management of the primary cardiac abnormality so that, insofar as possible, cardiac competence is restored.

In most patients with congestive cardiac failure, electrolyte abnormalities can be regulated by adequate use of digitalis, restriction of sodium in the diet, and restriction of the patient's activity so that the heart is not made incompetent by excessive demands on it. The degree of dietary sodium restriction necessary to maintain balance will be governed largely by the degree to which the patient's activity exceeds his cardiac competence. Rest is a potent diuretic. Exercise is a potent antidiuretic when it accentuates the manifestations of heart failure. If stimuli to the kidney to retain sodium are strongly operative (or cannot be alleviated by the aforementioned measures), then a strenuously restricted sodium intake will be necessary in order to avoid edema. Since the kidney, under the influence of a low renal blood flow, high venous pressure, and aldosterone, may excrete a small amount of sodium per day, the diet must contain no more than this amount if retention is to be avoided.

If adequate digitalization and dietary restriction of sodium are not carried out, potent diuretic drugs become a substitute for regulation of the primary factors responsible for the disease manifestations. If primary antidiuretic and antisaluretic influences go unregulated, then more forcible (pharmacological) measures must be used. However, these more forcible measures are directed toward correction of secondary manifestations of electrolyte derangement. It is a questionable practice to allow the liberal and continuous use of potent diuretic drugs as a substitute for adequate administration of digitalis, diet regulation, and restriction of physical activity.

As a practical matter, the selection of diet for the patient is influenced by several considerations. From our physiological studies, we conclude that a patient with heart failure and edema who exercises is likely to require either more dietary restriction of sodium or more vigorous diuretic-drug therapy, or both, than a patient who rests. Frequently, we must compromise because adequate rest to prevent edema may result in uneconomical and unhappy invalidism for the patient. How much one can substitute diuretic drugs for restriction of physical activity remains a problem to be solved in each specific case by trial and error. Also, severe restriction of sodium in the diet imposes on some patients an intolerable or impractical problem of procurement of the proper foods. Furthermore, the diet may be rejected on psychological grounds. Sodium-free salt substitutes may satisfy the appetite of some patients. Liberalization of the patient's sodium intake in many cases will necessitate heavier diuretic-drug therapy. The physician must carefully weigh the disadvantages of heavier drug therapy as against the advantages of more physical activity and more sodium in the diet. The electrolyte deranging aspects of the common diuretic drugs and the development of refractoriness are the disadvantages.

REGULATION OF ELECTROLYTES IN THE MANAGEMENT OF HEART DISEASE

Elliot V. Newman, M.D., Nashville, Tenn.

Regulation of electrolyte and water balance is the remarkable job of the kidney. However, when the kidney is not functioning properly, as in a patient with congestive heart failure, regulation becomes the difficult job of the physician. Thus, a knowledge of the intricate mechanisms influencing electrolyte regulation is necessary. In recent years, much has been learned about these mechanisms. Potent drugs, such as the carbonic anhydrase inhibitors and chlorothiazide, have been introduced. The discovery of aldosterone and the appearance of the experimental aldosterone blocking agents (spirolactones) are exciting developments. The important role of potassium with respect to cardiac and renal function has been elucidated; and perhaps we shall find that magnesium is important, too. Today there is more recognition of the importance of over-all metabolic balance derangements, as well as tissue abnormalities, at the cellular and extracellular levels. Since we now have powerful therapeutic weapons, let us see how we should use them.

Normal Electrolyte Regulating Mechanisms

The kidney selectively adjusts the output of sodium, chloride, potassium, bicarbonate, and water so that body composition and volume remain constant despite wide variations of intake. In order to do this job accurately, the kidney is able to regulate the output of each substance separately. For example, water balance generally is maintained separately from that of sodium, because sodium intake may vary greatly in proportion to water. The kidney depends on specific hormonal stimuli for its highly selective behavior. The antidiuretic hormone of the posterior pituitary causes water retention, and the electrolyte regulating adrenal hormone, aldosterone, causes sodium retention and potassium loss. Hormonal activity depends on stimuli arising from changes in body fluid electrolyte-water concentrations and, in some mysterious manner, on changes in the volumes or pressures in various body fluid compartments. Besides hormonal substances, renal excretion of electrolytes is influenced by changes in the renal blood flow and glomerular filtration rate, renal venous pressure, oxygen tension, acid-base loads, and mechanical intra-abdominal pressure.

An internal intercompartmental regulation of body composition keeps certain substances in higher or lower concentration inside the tissue cells. This gradient of concentration depends on the functional integrity of the body cells and their membranes. Thus, sodium and chloride are mainly extracellular and potassium is generally intracellular.

Misregulation of Electrolytes

A striking and distressing consequence of cardiac failure is the misregulation of electrolytes. Of primary importance is the kidney's failure to excrete sodium properly, whereas potassium is wasted. Generally, patients with congestive failure can drink water in liberal amounts and excrete it with no complications. However, as soon as sodium is added to the intake, water is retained. Thus, sodium retention is the primary defect and water retention is secondary.

This retention of sodium, which causes edema, may be due to many factors, including a diminished blood supply to the kidney and an excessive action of aldosterone, which is excreted in larger amounts than normal. Accumulation of fluid is accelerated by high venous pressure, which transfers retained sodium and water to the extravascular spaces. The spaces with the highest intravascular hydrostatic pressure and the lowest resistance of the tissue to stretching (integumental pressure) accept the edematous fluid. These spaces are determined largely by the elasticity of the skin and the patient's posture. In some cases (particularly in children), the fluid will run into the abdomen rather than into the lower legs as it does in ambulant adults.

Since aldosterone causes potassium loss concomitantly with retention of sodium, a potassium deficiency may develop if the intake is not adequate. Thus, an abnormal negative balance of potassium may accompany the positive balance of sodium. Deleterious consequences of potassium loss may ensue. For example, potassium depletion may weaken the action of the heart and limit the effectiveness of digitalis by potentiating its toxic effects. Breakdown of the intercompartmental arrangement of sodium and potassium may occur, so that sodium runs into body cells and the whole body becomes dilute (low sodium concentration in the serum). The extracellular fluid becomes alkalotic and the cells acidotic. Finally, depletion of potassium may cause a nephropathy characterized by proteinuria, inability to produce a concentrated urine, and a rising azotemia due to over-all renal insufficiency.

Another important but not often emphasized feature of misregulation of electrolytes in patients with congestive failure is the abnormality of the thirst mechanism. In spite of the hyponatremia, or, conversely, in spite of the high water retention (hyperhydremia), the patient may complain bitterly of thirst if water is restricted. The so-called low-sodium syndrome might be called the high-water syndrome. Actually, patients with edema have an abnormally high total amount of both sodium and

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From the School of Medicine, Vanderbilt University.

and phosphate excretion follow different patterns. Retention of sodium and chloride is specific and selective. Return to bed rest after walking restored ability to excrete sodium, chloride, and water. Thus, rest promotes diuresis, whereas exercise is antidiuretic.

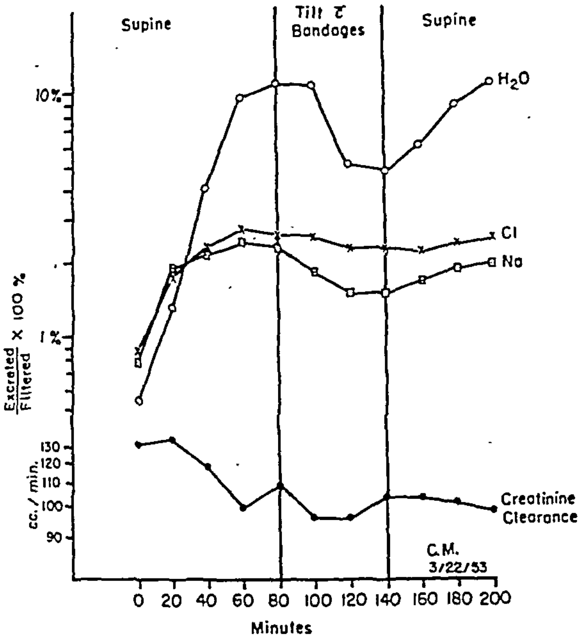

Fig. 3.—In normal subject, retention of sodium chloride in response to standing is almost completely obliterated by wrapping legs with elastic bandages before standing.

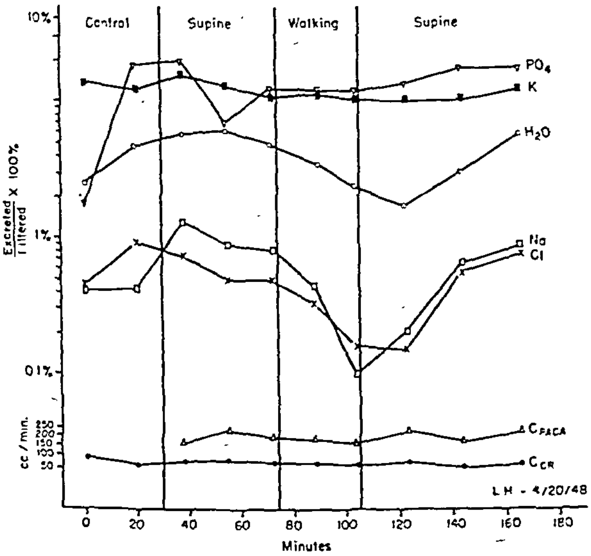

Fig. 4.—Effect of exercise in patient with congestive cardiac failure. C_{CR}=creatinine clearance.

Sometimes mercurial diuretic drugs with or without concomitant ammonium chloride administration will fail to cause diuresis and weight loss in a patient with severe congestive failure. In this circumstance, the addition of aminophylline may make the patient responsive to mercurial injection. Figure 5 illustrates the sharp drops in weight and the large accompanying rises in urine volume that are due to the combination of aminophylline with mercury injections, in a patient in whom on other days mercury injections alone were ineffective. It is thought that in some cases the cardiac output and renal blood flow are so low that mercury alone cannot cause a diuresis by its action on the tubular reabsorption of chloride and sodium.

The aminophylline was given intravenously, slowly (10 to 15 minutes' duration), in doses of 250 mg. three hours apart, two or three times daily. The mercurial, meralluride sodium, was given intramuscularly in a single dose of 2 cc. after the second dose of aminophylline. Aminophylline probably has a double action: First, it probably augments cardiac output and consequently renal blood flow by a direct effect on the myocardium and, second, it inhibits the reabsorption of sodium and water by the renal tubule cells.

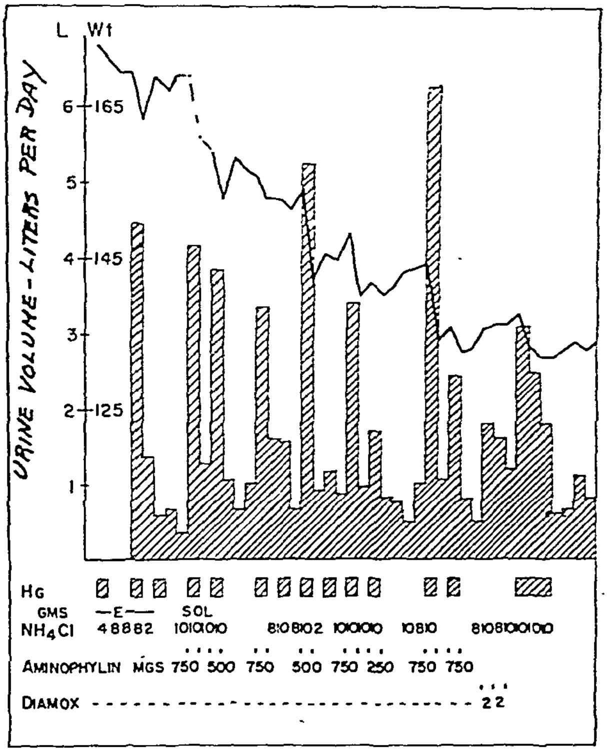

Fig. 5.—Effects of administering aminophylline in addition to mercurial diuretics.

It is also of some practical importance that enteric-coated preparations of ammonium chloride frequently are not absorbed. A solution of 10% ammonium chloride given by mouth can be tolerated fairly well if taken with food, and, although gastric irritation occasionally is an undesirable consequence, the solution is absorbed.

Greater freedom of activity, economic gain, better appetite, and cooperation of the patient are the advantages of the use of drugs. Each physician and dietitian must judge for the patient. Successful therapy often depends on proper education of the patient. There is often a great difference between prescribing a regimen and carrying out an effective, successful therapeutic plan.

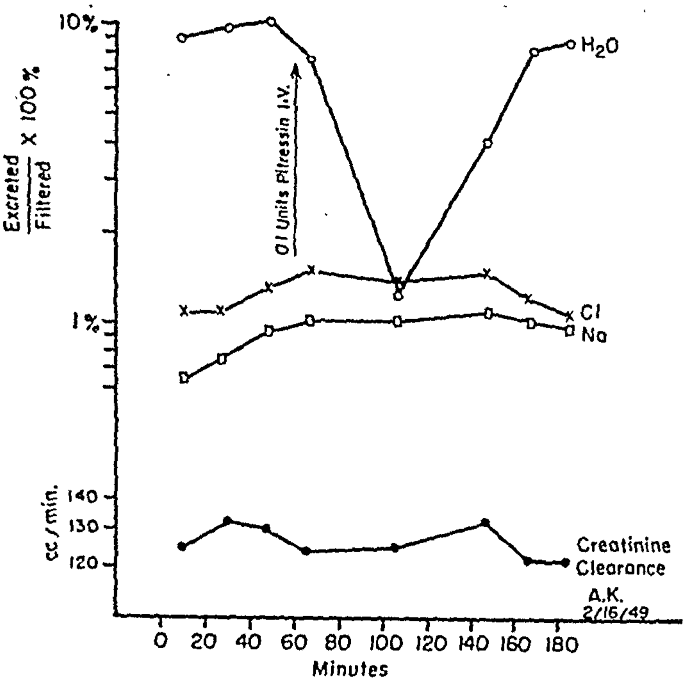

Fig. 1—Independence of water regulation from sodium and chloride, after injection of small physiological dose of antidiuretic hormone in normal subject.

Specific Regulation of Electrolytes

As seen in figure 1, the injection of antidiuretic hormone in a normal subject results in a 10-fold drop in water output, with no significant changes in sodium and chloride excretion. The ordinate scale is adjusted so that the same percentage change in excretion of each substance will cause an equal deviation on the graph. Creatinine clearance is measured as an index of glomerular filtration rate and as a check on the accuracy of the urine collections. The water, sodium, and chloride amounts are expressed as the percentage of the amount filtered by the glomeruli (as measured by creatinine clearance).

Figure 2 shows that, in a normal subject, the change from a supine to an upright posture (standing quietly but not passively, called "tilt" on the chart) causes a sharp drop in water, sodium, and chloride excretion. The mechanism of this renal response may be debated. It may be initiated by changes in renal circulation or by release of humoral substances which increase salt and water reabsorption by the renal tubule cells, or both. Whatever the mechanism, it operates both in normal subjects and in patients with congestive cardiac failure. An accentuation of this mechanism in the patient with congestive cardiac failure may be responsible in part for the excessive sodium and water retention. Output increases with resumption of the supine position. This is one reason for bed rest as a diuretic measure.

The exact changes in blood circulation which might initiate sodium and water retention are not known. The data in figure 3 imply that blood pressure–volume relationships are altered, causing renal retention. Other workers have suggested that hormonal control of sodium excretion is altered by blood or extracellular fluid volume shifts.

Figure 4 shows a striking and specific fall in sodium, chloride, and water excretion caused by walking slowly after being supine, with a gradual return to previous levels of excretion after resumption of the supine position. During the period marked "control" the patient was supine. The substance used for measurement of renal plasma flow (PACA or acetyl para-aminohippuric acid) was injected and a diuresis was established by the patient's drinking 120 cc. of water every half-hour. The patient had congestive cardiac failure but at this time was comfortable and not dyspneic at rest in bed. She was mildly dyspneic on walking.

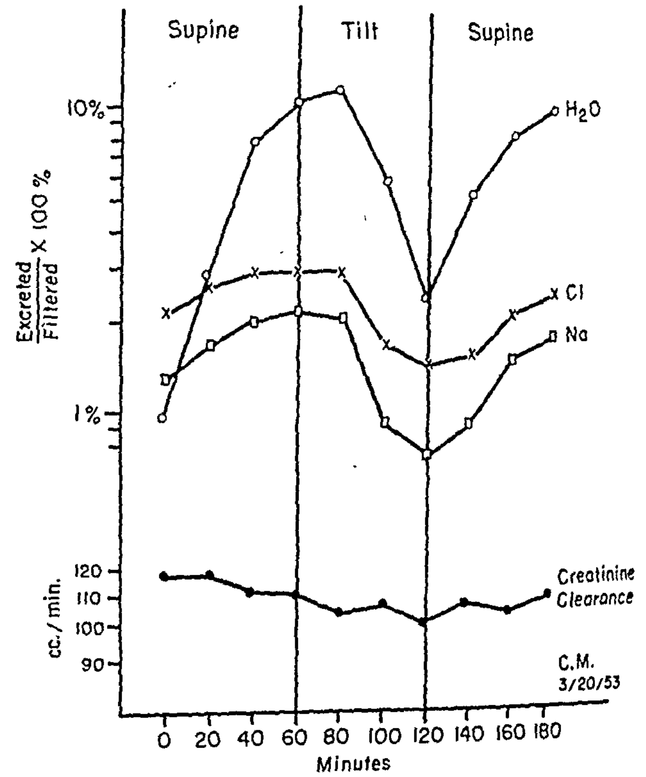

Fig. 2.—Regulation of electrolyte and water excretion in normal subject. This is sensitive to physical activity.

At rest, sodium and chloride excretion was at levels which would not require dietary sodium restriction to maintain balance. However, the tenfold drop in sodium excretion on walking represents a marked inability to excrete sodium under those conditions. This implies that the patient would retain sodium if she were allowed unrestricted physical exercise and sodium in the diet. *Potassium* sterone. They probably will be useful in conjunction with other diuretic drugs to augment the sodium loss while preventing the potassium wastage.

Figure 7 illustrates the effect on electrolyte excretion and body weight of aminoisometradine (Rolicton) and spirolactone (SC-8109). When given separately, neither drug causes a marked sodium loss, but together they cause a satisfactory moderate weight loss without loss of potassium. It is also noteworthy that the chloride loss is not excessive in proportion to the sodium loss, as is the case with mercury (see fig. 8). Aminoisometradine was given orally in four doses (400 mg.) during the day. Spirolactone was given orally (200 mg.) during the day.

Thus, in the future, spirolactones may augment diuresis and correct the deranging aspects of other diuretic procedures. At any rate, the spirolactones represent a *significant scientific advance in understanding* the mechanism of sodium retention in edematous states by revealing the role of the salt-retaining corticoids in patients with edema.

The question often arises whether administration of concentrated sodium chloride will correct low plasma sodium concentrations, and thereby relieve the edematous patient with congestive cardiac failure of his resistance to diuretic drugs. However, the problem is not treated so simply. The edematous patient has too much sodium (not really low total) but, in addition, has an even greater excess of water. Thus, one might just as well call the condition a "high-water" syndrome as call it a "low-sodium" syndrome. Furthermore, with the breakdown of the internal intercompartmental arrangement of electrolytes sodium enters cells in abnormal amounts, while potassium is lost from the cells.

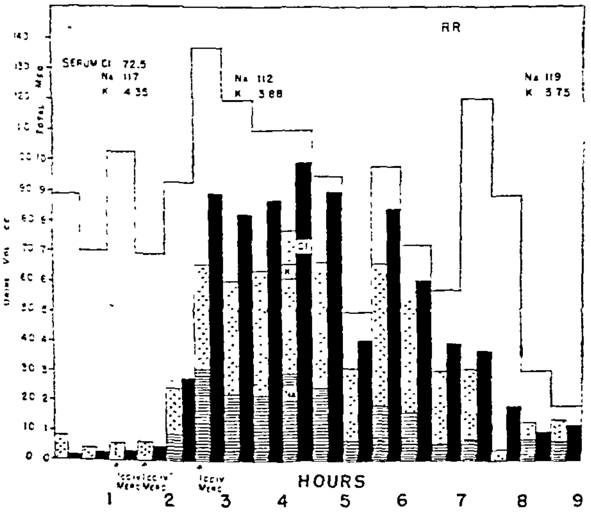

Fig. 8.—Electrolyte excretion response pattern after intravenous administration of meralluride, in patient with severe congestive failure with edema who was "resistant" to diuretic drugs.

Figure 9 demonstrates the futility of attempting to correct plasma concentrations by intravenous administration of large amounts of sodium chloride. This edematous patient was given enough concentrated sodium chloride so that if it all stayed in the extracellular fluid the plasma sodium concentration level should have risen to normal. During the two days of infusion the sodium concentration rose slightly, but, as soon as the infusion was stopped, there was no significant over-all rise in plasma sodium concentration. The infused sodium was not lost, because the total urinary output was negligible and did not increase. The only conclusion is that the sodium was distributed throughout a much larger amount of water than the extracellular fluid volume, namely, the total body water volume.

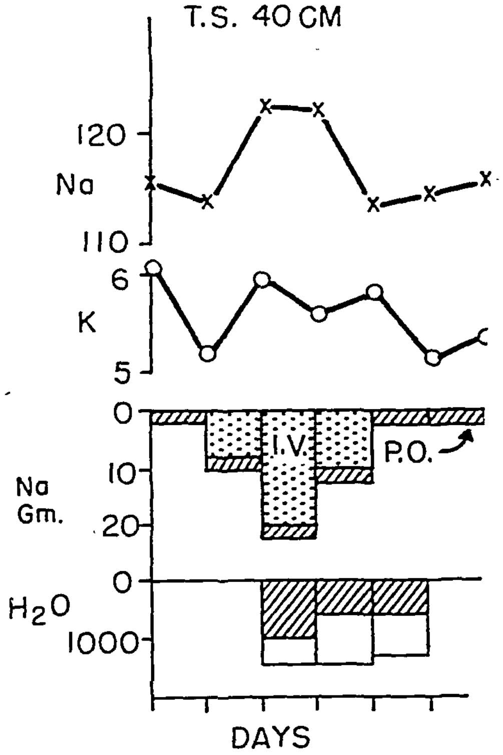

Fig. 9.—Results of giving large amounts of intravenous sodium chloride to correct plasma concentrations.

Summary

Congestive cardiac failure is primarily a disease of the hydraulic or circulatory system and secondarily a disease of metabolic derangement. It seems reasonable to direct therapy as much as possible to the primary system and not, if at all possible, to place disproportionate emphasis on treatment of the secondary metabolic manifestations. On the other hand, it is not entirely possible to separate hydraulic and metabolic events, because, while the hydraulic initiate the metabolic, the metabolic in turn worsen the hydraulic. Accumulation of sodium and water

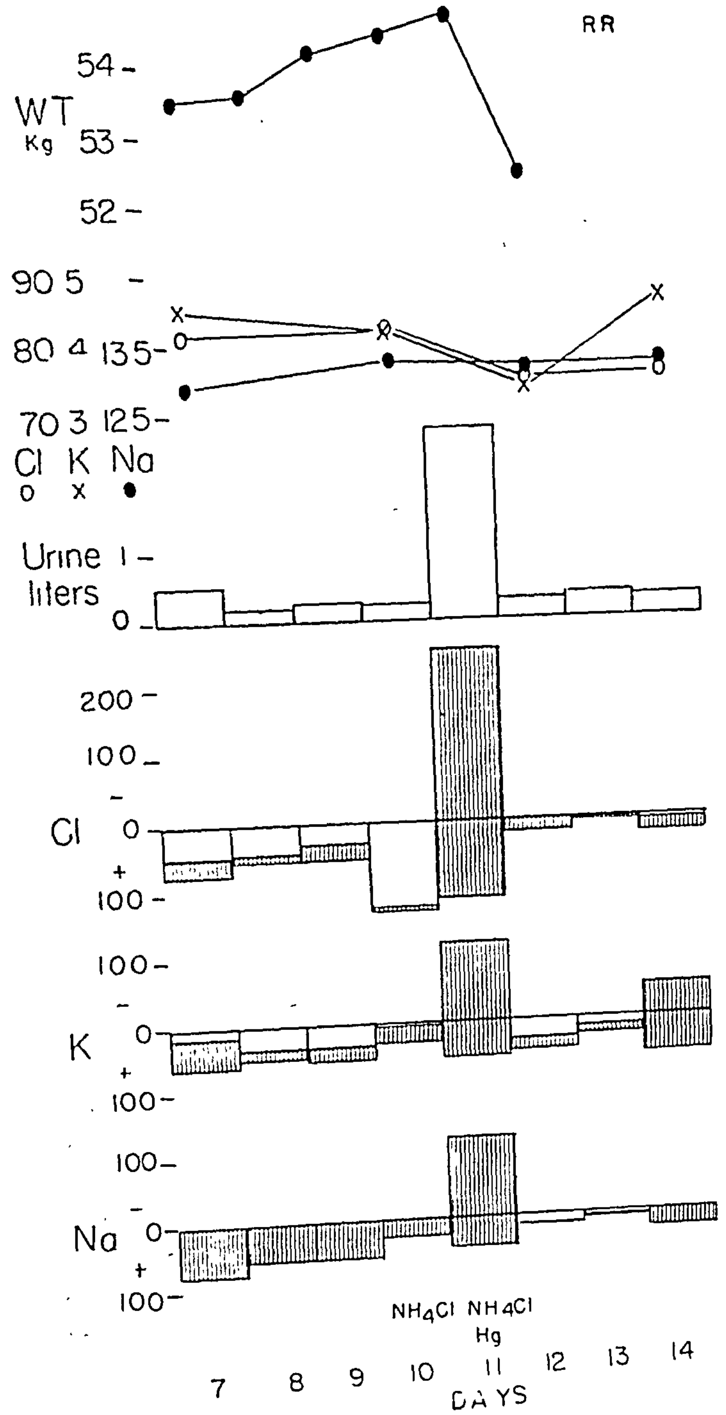

Fig. 6.—Accentuation of derangement of body electrolyte composition by use of mercurial diuretics and ammonium chloride.

Figure 6 shows the extensive diuresis and weight loss which occurred in a patient with severe chronic congestive failure and edema. However, the diuretic drugs merely accentuated the established pattern of potassium wasting. Potassium loss was as great as sodium loss. The drop in plasma concentration level of potassium caused muscular weakness and myocardial sensitivity to digitalis. In this patient, the diuretic regimen accentuated electrolytic derangements of cardiac failure, even though diuresis and weight loss were accomplished.

Each shaded block represents the daily output of chloride, potassium, or sodium in total milliequivalents. The intake is the distance from the zero line downward and from the intake line upward, so that the shaded area above the zero line is the negative balance for the day. Plasma levels of chloride, potassium, and sodium are plotted as milliequivalents per liter and weight in kilograms. Ammonium chloride was given as a 10% solution, to a total of 6 Gm. on the 10th and 11th days. The mercurial given on the 11th day was meralluride, 2 cc. intramuscularly.

Such responses to diuretic drugs raise the serious question whether extra potassium should be given to such patients routinely to protect against the consequences of hypopotassemia. In the future, we may have better mechanisms for diuretic therapy which do not cause serious potassium loss (fig. 7).

Figure 8 shows the electrolyte excretion response pattern in a patient after the administration of meralluride. The excretion of potassium is much greater than that of sodium. During the eight-hour period an insignificant amount of sodium was lost, but the amount of potassium lost was enough to cause further serious potassium depletion. This emphasizes that diuretic drugs, which do not cause a significant sodium and weight loss, may at the same time be causing serious potassium depletion.

Of great physiological interest and possibly of future practical value is the discovery of synthetic steroids which effectively block the sodium retention and potassium wastage caused by aldosterone in patients with congestive failure. These new steroid compounds, called "spirolactones," effectively block the action on the renal site of aldo-

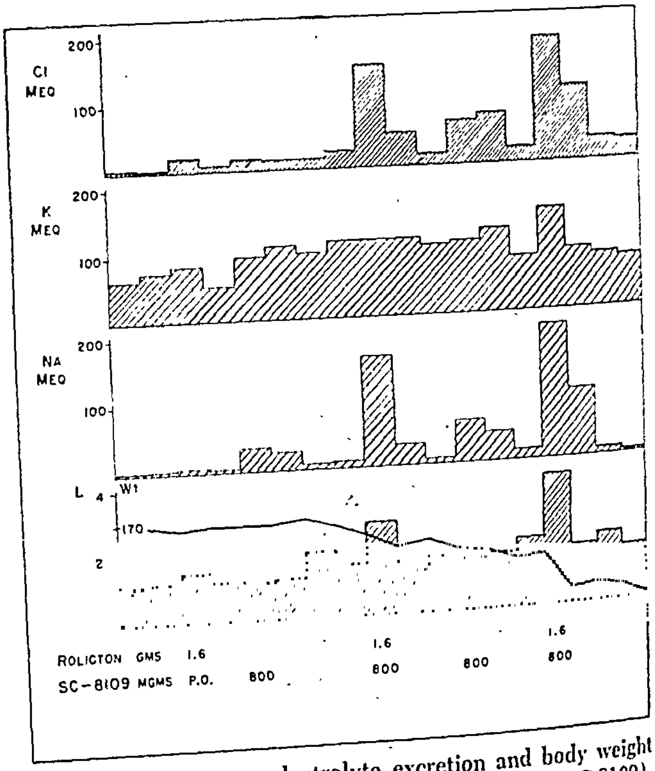

Fig. 7.—Effect on electrolyte excretion and body weight of aminoisometradine (Rolicton) and spirolactone (SC-8109), separately and together, in patient with moderate congestive failure with edema who lost potassium excessively when given mercurial diuretic or chlorothiazide.

mented. After being maintained for many weeks on the rice-fruit diet, 38 patients (76%) experienced significant lowering of supine diastolic pressure; 2 attained normal diastolic blood pressure levels during the control period and diet effected no further decrease; and 10 did not respond. Corcoran and associates[3b] used low-sodium dietotherapy with 14 patients. In four patients (29%) supine diastolic pressure fell to less than 100 mm. Hg. Other studies showed a greater or lesser percentage of responsiveness. For example, at the Hospital of the Rockefeller Institute,[8] 10 of 11 patients studied responded well to the diet therapy, whereas Chasis and co-workers[9] found no definite responders in a group of 12 patients.

Thus, it became apparent that low-sodium intake would decrease arterial pressure in some hypertensive patients but the studies did not reveal how such patients could be selected. Evidence indicates that patients with extremely high diastolic pressures generally do not respond as well as other patients to low-sodium therapy. In Kempner's series, prediet blood pressure average for the group who died during treatment was 226/147 mm. Hg. Of those patients who survived, there was no difference between the blood pressure average of the responding group (199/116 mm. Hg) and the nonresponding group (195/114 mm. Hg). Watkin and associates found a clear difference between responders and nonresponders. For the group of 38 who responded to the diet, the blood pressure average for the last three weeks of the control period was 193/108 mm. Hg, and for the 10 persons who did not respond, blood pressure during a similar period averaged 211/135 mm. Hg. Corcoran and co-workers[3b] did not find such a difference between the prediet arterial pressure levels of responders and nonresponders. What little evidence there is is suggestive only and seems to pale in significance when one realizes the number of patients with malignant hypertension who were improved greatly by low-sodium diets.

Chlorothiazide, is not of itself, a potent antihypertensive drug.[6] Finnerty and associates[10] suggested that when it is used alone it is effective in about 20% of patients with moderately severe hypertension and ineffective in those with severe hypertension. Another study[11] also suggests that diastolic blood pressure level may influence responsiveness. Chlorothiazide was administered to 15 patients for periods of 3 to 14 days. Among 12 patients who responded, supine blood pressure averaged 168/108 mm. Hg before and 145/96 mm. Hg during treatment. For the three nonresponders, control pressure averaged 218/133 mm. Hg and treatment levels were 208/126 mm. Hg. Since most of the early interest in diuretic therapy of hypertension has been directed toward its effect on responses to other antihypertensive drugs,[6] it is not known yet whether diuretics are as effective a depressor as low-sodium diets.

Changes in Plasma and Extracellular Fluid Volumes and Total Exchangeable Sodium Content

Since low-sodium diets and diuretics cause negative sodium and water balance, we may expect measurable decreases in body sodium content and plasma and extracellular fluid volumes during these regimens. During investigations of low-sodium dietotherapy, several workers attempted to relate decreases in arterial pressure to fluid and electrolyte shifts. Although a positive correlation was not obtained, investigations into antihypertensive effects of chlorothiazide suggest that decreases in plasma and extracellular fluid volumes are basic to the mechanism of its action and, therefore, probably to low-sodium diets.

The speed with which diuretics or low-sodium diets, or both, can decrease plasma and extracellular fluid volumes seems to depend on the rapidity with which maximum negative sodium and water balance is reached. Thus, Lyons and associates[12] found a 14% mean decrease in plasma volume in 10 normotensive subjects after three to four days on a low-sodium diet with the administration of 9 Gm. of ammonium chloride daily. Murphy[13] found a 10% decrease in hypertensive patients between the 10th and 14th weeks of a rice-fruit diet. Harris and co-workers[14] attempted to relate blood pressure changes of normotensive and hypertensive subjects to the rapid fluid and salt loss occasioned by three days of low-sodium diet with the administration of 9 Gm. of ammonium chloride daily and a mercurial diuretic given on the third day. After this rugged regimen systolic pressures fell slightly and diastolic pressures rose slightly in both groups. Murphy obtained decreases of arterial pressure in 13 of the 16 hypertensive patients on the rice diet but could not relate therapeutic responses to plasma volume changes. A similar lack of correlation was found by Dole and others[3c] and by Corcoran and others[3b] in explorations of the possible mechanism of action of low-sodium diets.

Megibow and associates[15] suggested that injections of mercurial diuretic during the early phase of low-sodium dietotherapy would hasten a decrease in arterial pressure which probably was due to augmented sodium loss. Dole and co-workers[3c] measured total exchangeable sodium in five patients during periods of gradual sodium depletion and sodium repletion. They found that total exchangeable sodium contents fell with low-sodium dietotherapy and rose when sodium was added. All patients responded to the diet with significant decreases in arterial blood pressure. These workers were impressed with the fact that losses in body increases vascular congestion, heightens venous pressure, and adds to cardiac dilatation and respiratory distress. Under these circumstances, vigorous diuretic therapy directed to the secondary manifestation of sodium retention may ameliorate primary hydraulic abnormalities. The purpose of all measures directed to regulation of electrolyte levels is to maintain the best degree of cardiac competence and circulation. Failure of diuresis or "resistance" to diuretic drugs is really a problem of intractable or irreversible cardiac failure. Some deranging complications of diuretic therapy are due to unrelieved or severe manifestations of the primary hydraulic cause, which is malfunction of the heart.

The metabolic lesions of congestive failure are sodium retention, potassium loss, water retention, abnormal thirst, and abnormal concentrations of electrolytes in tissue cells as well as extracellular fluid. Some of the therapeutic measures and diuretic drugs may worsen some of the lesions (potassium loss and hyponatremia) while correcting others (sodium retention and edema). The recently discovered spirolactones, which specifically block the action of aldosterone on renal sodium retention and potassium loss, in the future may be valuable diagnostic and therapeutic adjuncts in the management of edematous patients.

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DIET AND DIURETICS IN THE TREATMENT OF HYPERTENSIVE CARDIOVASCULAR DISEASE

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In the 1920's, Allen[1] recognized the importance of low-sodium diets in the treatment of hypertension, but his approach did not gain wide acceptance at that time. Twenty years later Kempner[2] used the rice-fruit diet, but he did not emphasize its sodium-restrictive aspects. However, subsequent use of low-sodium diets that supplied adequate protein and of rice-fruit diets which were supplemented with protein amply demonstrated that sodium restriction was the only important factor.[3]

Interest in low-sodium diet therapy was intense during the late 1940's. Good clinical studies, with adequate prediet control periods, established the antipressor potential of sodium restriction in a substantial proportion of hypertensive patients studied.[4] Disappointingly, the mechanism of this antihypertensive effect was not explained, but an important background of information developed concerning physiological changes that accompany sodium restriction.

About 1951, interest in dietary treatment of hypertension began to lag, partly because few patients would follow the rigid program necessary for therapeutic success and partly because antihypertensive drugs with long-range effectiveness had become available. Low-sodium diets came to be used primarily for hypertensive patients with congestive cardiac failure, even though sodium restriction was thought to increase depressor responsiveness to ganglion-blocking drugs.[5]

Development and wide use of the orally effective diuretic, chlorothiazide,[6] again focused attention on the role of sodium in maintenance of hypertension. Shortly after introduction of this drug, it became apparent that any diuretic agent, such as a mercurial diuretic or chlorazanil, could duplicate the effects of chlorothiazide, either alone or in combination with other antihypertensive drugs.[7] Because of similarities between low-sodium diets and diuretic therapy, it seems timely to review our knowledge concerning the changes that occur during such treatments and to suggest a possible mechanism of their action.

Antihypertensive Effects of Low-Sodium Diets and Diuretics

Results from Kempner's extensive study showed that low-sodium diets lowered arterial pressure and reversed signs of progressive arteriolar disease in some hypertensive patients. Because carefully controlled studies with as many as 500 patients are difficult to achieve, subsequent investigations were carried out by others in smaller groups of patients to establish the depressor potential of such diets and to explore the mechanism of antihypertensive effects.

In Kempner's group of 500 hypertensive patients, 311 (62%) sustained arterial pressure decreases, 163 did not respond, and 26 died during diet therapy. Watkin and co-workers[3a] studied 50 patients who were observed during long control periods so that prediet blood pressure levels were well docu-

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Chlorothiazide administration for 3 to 14 days caused changes in renal functions similar to those observed during low-sodium diet therapy.[11a] Increases in blood urea concentration of a degree seemingly out of proportion to the fall in GFR suggested some extrarenal effect of chlorothiazide on nitrogen metabolism. Urea retention has been noted in other reports.[6]

Responsiveness to Antihypertensive Drugs

When rigid low-sodium dietotherapy was discarded as antihypertensive drugs of long-term potency became available, the effect of diets on responses to these drugs received no emphasis. Smirk and Alstad[5b] presented slight evidence that sodium restriction improved responses to ganglion-blocking drugs. Brust and Ferris[5a] suggested that the depressor effect of tetraethylammonium chloride (TEAC) in hypertensive patients was enhanced by withdrawing sodium from the diet.

However it was not until the introduction of chlorothiazide that a clear relationship was demonstrated between sodium and water balance and drug responsiveness in hypertensive patients. The first reports described a greatly enhanced effectiveness of antihypertensive drugs when patients were given this diuretic.[6] Shortly, it became obvious that such effects could be duplicated with other saluretic agents.[7]

Early studies by Tapia and associates[16] suggested that a decrease in plasma volume might be the important factor in the chlorothiazide-enhanced effectiveness of ganglion-blocking drugs. The amount of a ganglion-blocking drug required was decreased during chlorothiazide-induced oligemia and returned to control levels during a period of sodium repletion, which caused reexpansion of plasma volume. However, these findings did not eliminate the possibility that decreases of total body sodium content are the determining factor in this enhanced responsiveness. Later, Wanko and Freis[23] described a decreased pressor response to a norepinephrine infusion and increased depressor response to trimethaphan camphorsulfonate during chlorothiazide treatment. These responses were returned to prediuretic levels by administration of salt-free dextran. We found that the depressor effects of TEAC were enhanced after several days of chlorothiazide treatment[11b] and that the ganglioplegic drug had the ability to lower the increased peripheral resistance that had developed during administration of the diuretic.

Suggestions Concerning a Mechanism of Action

From the aforementioned studies, it is obvious that low-sodium dietotherapy and diuretic therapy have much in common: Both cause negative sodium and water balances resulting in decreases of body sodium content and of plasma and extracellular fluid volumes; both cause decreases in arterial pressure. Although the exact explanation for this antihypertensive effect is not known yet, there is enough evidence to suggest a common mechanism of action.

Oligemia in animals, produced by bleeding, causes an increase in vasoconstrictor impulses[24] and also greatly enhances the depressor effects of TEAC. Oligemia in normotensive and hypertensive subjects likewise increases responsiveness to a variety of depressor agents.[25] Furthermore, we have found that chlorothiazide increases peripheral resistance, presumably because of oligemia, and that this vasoconstriction can be diminished by TEAC. Accordingly, it seems likely that during the early phase of low-sodium diets or diuretic therapy, decrease of intravascular volume due to negative sodium and water balance increases the autonomic nervous system's participation in maintaining the arterial pressure level and, therefore, enhances responsiveness to antihypertensive drugs, particularly those that act on the nervous system. Although applicable to the early phases of oligemia, this suggestion conflicts with the findings of a normal cardiac output and decreased peripheral resistance in two patients after weeks on a low-sodium diet.[3a] Acute oligemia decreases cardiac output, but when oligemia is maintained for prolonged periods, homeostatic mechanisms should come into play which would result in a readjustment of pressure-flow relationships. More evidence is needed for confirmation of this suggestion.

If intravascular volume is important in the maintenance of the hypertensive state, the question arises whether it is elevated in hypertensive patients. Such increases have not been found, but, since the vascular tree is a closed system, a decrease of arterial capacity by arteriolar narrowing could result in relative hypervolemia. This, then, indicates that intravascular volume is important and disregards the importance of body sodium except as it may enable maintenance of that volume. Tobian and Binion found that the sodium content of the arterial wall is increased in experimental and clinical hypertension. Friedman and associates[27] suggested that the sodium gradient between the arteriolar cells and the interstitial fluid is an important determinant of vascular reactivity. These suggestions may bear significantly on the mechanism of action of low-sodium diets and diuretics in the treatment of hypertension but, at the present time, our methods for measuring intracellular and extracellular electrolyte concentrations are not adequate for clinical evaluation.

Summary

Favorable responses of hypertensive patients to oral diuretics have reawakened interest in the role of sodium and water in maintenance of the hyper-

water seemed small in comparison to the amount of sodium lost. They suggested that water from the extracellular space moved intracellularly and increased cellular hydration. They concluded that the low-sodium diet might exert its beneficial effect by this increase in cellular hydration.

Early in the clinical trials of chlorothiazide, Tapia and co-workers [16] found that diuresis and saluresis consistently decreased plasma volume and that decreases were greatest in patients on low-sodium diets. Wilson and Freis [17] confirmed the observations of chlorothiazide-induced oligemia. Extending their study to include patients on long-term chlorothiazide treatment, they found that plasma and extracellular fluid volumes remained below normal, and that total exchangeable sodium contents decreased early but tended to rise above control levels after months of therapy. Macleod and co-workers [18] studied daily changes in plasma volume of hypertensive patients given chlorothiazide for three days. Maximum decreases were observed on the first day but arterial pressure changes did not occur until the second and third days.

From these studies, it is apparent that low-sodium diets or diuretics, or both, decrease plasma and extracellular fluid volumes and total exchangeable sodium. However, it is not clear whether the fluid change or the sodium change, or both, are important. Although no immediate causal relationship between these changes and decreases in arterial pressure has been described, it would be naive to deny the possibility of an indirect association.

Changes in Heart Size and Hemodynamics

Reductions in heart size repeatedly were observed in hypertensive patients on low-sodium diets,[10] even in patients who obtained no fall in arterial pressure. Murphy [13] and Watkin and associates [3a] found a positive correlation between decrease in heart size and decrease in plasma volume, although there was no correlation between changes in diastolic blood pressure and plasma volume. Harris and co-workers [14] further emphasized that diastolic blood pressure is not the only important factor in determining heart size. They found that rapid salt and water loss caused a decrease in the transverse cardiac diameter of both normotensive and hypertensive persons. This is not surprising, since Sjöstrand [20] demonstrated that heart size depends, in part, on total blood volume. Other observations made during rapid diuresis [14] were that systolic pressure fell slightly, diastolic pressure rose slightly, venous pressure fell, and pulse rate rose. A suggested explanation of these findings was that the decline of plasma volume decreased central venous volume and, therefore, venous return to the heart. Such changes would decrease cardiac output and systolic pressure. They suggested that these factors caused an increased vasomotor tone, which was expressed by the increased diastolic pressure. Although changes in these various functions were small, they were consistent enough to allow for such a suggestion. Another investigation reports a significant decrease in cardiac output and an increase in peripheral resistance in hypertensive patients after three to six days of chlorothiazide administration.[11a]

The effects of low-sodium diets on cardiac output and peripheral resistance have not been studied sequentially. There is only slight information from Watkin's study.[3a] In three hypertensive patients, cardiac output was normal after 9 to 18 weeks on a rice-fruit diet. Two patients had considerably lower arterial pressure levels, so their total peripheral resistance was reduced; in the third patient it was unchanged. It is apparent immediately that these data are too scanty for an analysis of hemodynamic changes during low-sodium dietotherapy, but they have been included here because they are not in accord with previous observations [11b] and other findings.[14] Possibly a slower salt and water loss, such as would occur during low-sodium therapy, without diuretics, might not cause a depletion of plasma volume rapidly enough to depress cardiac output. But low-sodium diets alone decrease plasma volume to the same degree as do courses of chlorothiazide that have been shown to depress cardiac output. Perhaps the vascular system is capable of dynamic readjustment either to avoid or to eliminate chronically decreased cardiac output and increased peripheral resistance.

Changes in Renal Function

Both normal and hypertensive persons being given low-sodium diets experienced decreases in renal blood flow and glomerular filtration rate (GFR).[21] For the most part, the GFR was depressed out of proportion to the depression of renal blood flow, resulting in a decrease of filtration fraction. Urea retention also was observed, particularly in patients who experienced rapid diuresis. The mechanism of these changes remains uncertain. Harris and associates [14] suggested oligemia as the explanation since they found a relationship between the amount of weight loss and decreases of renal plasma flow and GFR. To replete plasma volume, Weston and co-workers [21a] gave 1,100 ml. of albumin to two patients with diet-depressed renal function. Although renal blood flow was increased, the GFR remained low. In one patient, the GFR rose after the administration of 300 ml. of 0.78% sodium chloride solution. We do not know if plasma volume or total sodium is important, but we do know that sodium supplements given during low-sodium diets will restore depressed renal functions to normal.[22]

DIET IN TREATMENT OF ASYMPTOMATIC CORONARY HEART DISEASE IN MILITARY PILOTS

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In a man-plane-weapons system, the limiting factor in the success of a mission often is ascribable to the human element. This limitation is sometimes referable to the cardiovascular system, and coronary heart disease poses the most important single problem. We are concerned over the facts that coronary heart disease may limit the flier's career and that the occurrence of acute coronary incidents in pilots aloft constitutes a hazard.[1] Our inability to predict these incidents is at once frustrating and disturbing. We can deal only in the likelihood of their occurrence. In the case of hypertensive cardiovascular disease an indicator, hypertension, is present long in advance of circulatory failure. A comparable indicator, coronary atherosclerosis, rarely is detectable prior to involvement of the myocardium. Moreover, even in the presence of coronary artery disease, we know little concerning the factors which precipitate acute coronary incidents.

Problems of the pilot must be considered from the standpoint of his entire career. At the induction center, is it possible to identify applicants for flight training who are likely to experience acute coronary incidents early in life? Should an attempt be made to control the diet of fliers prior to evidence of coronary heart disease? What constitutes definite evidence in the absence of myocardial infarction? How should fliers with asymptomatic minimal coronary heart disease be treated? The following discussion is based on my experience at the Naval School of Aviation Medicine in Pensacola and is concerned with identification of these problems and the attempts that are being made to deal with them.

Identification of High Predisposition to Coronary Heart Disease

An attempt is being made to develop a "master index" of susceptibility to coronary heart disease, taking into account such factors as age; race; heredity; personality traits; height, weight, and build; metabolic factors; arterial blood pressure; and abnormalities disclosed in the course of a medical examination. Even if all known factors have etiological significance, the problem still is complicated, not only by the intercorrelation of known factors but also by the influence of unforeseen or unknown factors. In order to be worthwhile, the index must be sufficiently reliable to identify applicants who should not be accepted. Although there is no such index at present, efforts to develop one are worth making, both to increase our general knowledge and to help us create a more effective program of preventive medicine.

Many investigators have been interested in blood lipid levels as indicators of a predisposition to coronary atherosclerosis and coronary heart disease. Beischer[2] reported on serum lipoprotein determinations carried out on 275 naval aviation cadets whose mean age was 21½ years. Gofman's technique was used, by which serum lipoproteins are quantified and classified according to their flotation rates in the ultracentrifuge. From these values, an atherogenic index is derived wherein the Svedberg flotation (S_f) classes 20-400 are weighted × 1.75. Beischer noted that 11 men (4%) had an "atherogenic" index above 80, which was two standard deviations above the mean, and 6 men had a value above 95, which was three standard deviations above the mean. Meanwhile, Mitchell,[3] in a cardiovascular survey carried out on civilian workers at the Pensacola Naval Air Station, did not find any values above 60 in women who had not passed the menopause. In another study, Beischer and Born[4] carried out fat tolerance tests on 10 representative subjects who ate one quart of ice cream (20% fat). The serum cholesterol level and lipoprotein fractions (Gofman's method) were determined before eating and at 1, 4, and 24 hours after eating. Serum cholesterol values did not change significantly after the fat-loaded meal, but the atherogenic index rose in all subjects. The percentage increase was greatest for the S_f 100-400 class and least for the S_f 0-12 class. Even in this small number of persons, individual variability with regard to the time course of the changes in the serum lipoprotein values was so great as to suggest that the test may have value independently of any single determination. Further studies exploiting the fat tolerance test will be reported soon.[5] In comparing Gofman's test and the serum cholesterol test, there seems to be more individual variation in the atherogenic index than in the values of the serum cholesterol. In addition, the atherogenic index seems more readily influenced as a result of change in diet, exercise, and other factors. Inasmuch as there is a good opportunity for follow-up studies in the pilot group, we expect to obtain information dealing with the validity of these tests and their relative value.

It is altogether likely that by the time we can identify, at the induction center, those persons in whom coronary heart disease will develop early in life, this condition will be regarded as a cause for rejection rather than as a challenge in treatment.

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tensive state. Both low-sodium diets and diuretics cause diuresis and saluresis; both decrease plasma and extracellular fluid volumes and total exchangeable sodium; both may decrease arterial pressure; and both increase responses to antihypertensive drugs. Oligemia increases vasomotor tone and enhances effects of vasodepressor agents. Evidence is presented to suggest that oligemia induced during early phases of low-sodium dietotherapy or diuretic therapy is the basic mechanism of the antihypertensive effects of these regimens. There is not enough evidence to indicate whether this mechanism is operative during long-term therapy.

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on the basis of electrocardiographic findings. We are relying on follow-up studies to validate the significance of alterations that are doubtful.

The consequence of our evaluations is that we identified a group with asymptomatic coronary heart disease of minimal severity. These men were middle-aged, intelligent, with good mental discipline, and highly motivated in terms of their Navy careers. Most of them were married. We have no evidence that flying stress leads to the early appearance of coronary heart disease.[9]

Treatment

The general plan of treatment is the same for everyone, with few exceptions. The central theme is good hygiene, a minimum of alterations in the flier's way of life, and moderation in all things. Sufficient time is spent with each man to familiarize him with every important aspect of the program. Our objectives are maintenance of good nutrition, control of weight, reversal of evidence of coronary heart disease, and improvement in factors ordinarily regarded as predisposing to coronary atherosclerosis. A few comments will indicate the general nature of our program.

During the period of adjustment to the new regimen, sufficient time is taken to answer all questions, tailor the program to individual needs and desires, and encourage prospects of long-range benefits. It is emphasized that "the diet" is nothing more than a sensible way of eating. In addition to printed forms listing the composition of different foods and their use in the preparation of typical meals, a book is furnished or recommended to serve as a reference.

With regard to fats, the general instruction is to eliminate hard fats from the diet, insofar as possible, and, to a judicious degree, substitute oils. Only in a few instances is there any attempt to control the cholesterol intake more specifically. The need for an adequate amount of protein is emphasized and the principal sources of high-protein low-fat foods are given. Skim milk is recommended in preference to whole milk. Carbohydrate foods are classified roughly according to their caloric content, and carbohydrate foods with high fat content are listed. No attempt is made to have the men count calories, and a snack between meals is recommended to prevent hunger pangs.

Special Considerations.—The all-purpose vitamin pill provided by the Navy is recommended in every case. Additionally, for older persons on a very low-fat diet, 50,000 units of vitamin A also is recommended. It might be mentioned in passing that, in older persons on a very low-fat diet, certain wart-like skin lesions disappeared after the administration of vitamin A alone or vitamin A and an increased amount of oil in the diet. Unsaturated fatty acids in capsule form were given a trial but are not recommended generally. Drugs for reducing the appetite are used infrequently. Two points are made with regard to alcohol, namely, its caloric value and its possibly unfavorable effects on dietary discipline.

The question of exercise always comes up but it seldom presents a problem. Nearly all subjects take some form of regular exercise; occasionally, it is necessary to discourage certain strenuous types of exercise, but commonly the men are encouraged to spend more time exercising.

Results

Failure.—Reasons for failure of treatment are traceable in general to (1) the "lifelong" duration of treatment, (2) the difficulty of providing a diet out of line with what might be termed the "national diet," (3) the problem of appetite, and (4) the poor relationship between "treatment and effect" on a short-term basis. In individual instances, changing doctors, changing stations, retirement from the Navy, personal discouragements, and many other factors are responsible for dietary "back-sliding."

Success.—Elements contributing to success include (1) long-range rather than short-range objectives, for example, the prevention of disabling coronary heart disease as against the desire to pass an examination for promotion; (2) preference for foods recommended in the diet and sometimes an active distaste for fat-rich foods; (3) increase in exercise tolerance; and (4) satisfaction in doing something beneficial.

Summary

Some accidents occur aloft because of acute coronary incidents. Physicians have begun to identify the men most susceptible to these incidents and to institute preventive treatment for them. This treatment includes maintenance of good nutrition and control of body weight. Motivation to follow a recommended regimen is high, especially after definite evidence of coronary disease is established. In order to improve our identification process, we have been working on a "master index" of susceptibility to coronary diseases. However, while we have a good clinical indicator for hypertensive heart disease, we are handicapped because we cannot determine the rate and extent of the atherosclerotic process. Service-wide revision of the present high-fat diet may be justified because of the tendency of our young men to gain weight and the high incidence of atherosclerosis among them in postmortem findings. Until such time as we have good preventive therapy, we must make use of what is at hand, and control of body weight is a worthwhile objective.

NOTE: With regard to the supplementary administration of vitamins mentioned in the section on "Treatment" under "Special Considerations," the Council generally does not recommend the use of vitamins in this matter. It is the opinion of the

Even if the decision were made to treat such persons, it would be a difficult task. One reason is that young men volunteering for a hazardous profession are not much concerned over something as remote as degenerative diseases. Moreover, the special effort needed to provide them with a suitable diet and to keep them under medical surveillance would constitute a formidable undertaking. This could be done only on a service-wide basis. Considerable thought has been given to the feasibility of such control over the present diet, which is very rich—about 50% of the calories in this diet are derived from fat. Whether feasible or not, it certainly is possible not only to reduce the total amount of fat but also to substitute oils for some of the hard fats. The cost of food and the amount of labor in preparation would be somewhat greater, but long-range economic benefits might well offset these increased costs. Certainly, fears expressed regarding acceptability of this diet are not well founded. In short, it might prove to be a noble experiment in preventive medicine.

Diet Control Prior to Appearance of Coronary Heart Disease

Before attempting to answer the question whether diet should be controlled prior to the appearance of coronary disease, two points deserve mention; the first concerns the need for weight control and the second the frequency of occurrence of coronary disease in young fliers.

It is well known that even young men begin to put on weight. In a follow-up study involving 677 aviators who first were examined in 1940[6] and again 12 years later,[7] at which time their mean age was 35.2 years, 495 had gained an average of 19.97 lb. (9.07 kg.) in weight, while 42 had lost an average of 10.71 lb. (4.9 kg.). The weight of the remaining 140 aviators was about the same. Moreover, men in their 30's have an increase in serum cholesterol values, and some have a rise in blood pressure.

In the clinic and in the clinical follow-up of the aviators,[7] evidence of coronary heart disease rarely was found in the group of those under 35 years of age. On the other hand, postmortem findings indicate that moderate to advanced coronary atherosclerosis is found in 10 to 15% of men aged 20 to 24 years, the percentages increasing with age thereafter.[1] Thus, it might appear as if there were a discrepancy between the findings in the clinic and those in the pathology laboratory. One explanation is that these groups do not represent a random sample, since persons with moderate to advanced atherosclerosis are more likely to die aloft. This would explain the high incidence of atherosclerosis in those who died and the relatively low incidence in those remaining. However, if the sampling is reliable, why is it that so many young men with coronary atherosclerosis do not exhibit any evidence of coronary heart disease over long periods of time? Perhaps it is due partly to periodic activity and regression of the atherosclerotic process; partly to the fact that vasodilation with exercise still is possible in the young; and, above all, to the fact that a considerable narrowing of the coronary vessels still may provide adequate blood supply to the heart. Nevertheless, the findings of the pathologists suggest that it is necessary to reexamine all of our conclusions based on the premise that coronary heart disease is virtually ruled out in men under 30 years of age.

In my opinion, the high incidence of coronary atherosclerosis in young fliers and their tendency to gain weight justify attempts at weight control. With the proper indoctrination and encouragement, young fliers might avoid the weight gain which commonly begins between 20 to 30 years of age. In a recent study, pilots of high-performance jet aircraft were asked whether they would look with favor on factual propaganda regarding control of body weight. Nearly all indicated they would welcome such information, and a few were enthusiastic. These pilots were between 25 to 35 years of age, nearly all had homes of their own in which dietary measures could be put into effect, and all were highly motivated toward a lifelong career in aviation. However, great difficulties must be overcome before any efforts are likely to be successful. These problems will be mentioned in a later section.

Identification of Coronary Heart Disease in Absence of Myocardial Infarction

The question of coronary heart disease is sometimes raised as a result of findings disclosed during "routine" examination. Complaints are rare, and symptoms which might be referable to myocardial ischemia are not only infrequent but vague. In most instances, the problem arises as a result of some abnormality observed in the electrocardiogram. Alterations in T waves and S-T segments comprise most of the difficult problems. Definite evidence of coronary heart disease, regardless of the degree of involvement, is held to be significant inasmuch as it is associated with an increased likelihood of an acute cardiac incident. A conclusion must be reached that the pilot is either fit or not fit to fly. Unfortunately, medical evidence is not always this definitive. We use a variety of special tests in an effort to arrive at a definitive diagnosis, but the single most helpful test in our experience has been the work electrocardiogram.

Recently, Allebach and I[8] reported our experience with the work electrocardiogram and stressed the importance of graded exercise. Varying the work load was helpful not only in a qualitative sense, that is, in establishing the diagnosis of coronary heart disease, but also in a quantitative sense, by which I mean in estimating the degree of coronary insufficiency. We have been conservative in making a definite diagnosis of coronary insufficiency completion of the test. An excess of 5 Gm. of fat in the stool per day is considered abnormal in a person with a daily intake of 50 to 100 Gm. of fat.[1] It should be pointed out that there is some endogenous fat in the stool, which occasionally may constitute a large portion of the fecal fat.[2] Nevertheless, the fat balance study as currently employed is generally accepted as the most reliable method of determining the amount of fat in the stool and the presence or absence of steatorrhea.

Radioactively Tagged Lipids.—In recent years, the availability of radioactively tagged lipids has offered a new approach to the problem. With use of a test meal containing radioiodine (I^{131})-tagged triolein, characteristic and reproducible curves representing blood levels of radioactivity may be expected in the normal subject,[3] and less than 5% of the radioactive content of the test meal is recoverable in the 48-to-72-hour collections of the stool.[4] Recently, Grossman and Jordan [5] found a consistent correlation between chemical fat balance determinations and the radioactive content of the stool after ingestion of the test meal.

In patients with frank steatorrhea, regardless of the cause, blood levels of I^{131} are depressed and the radioactive content of the stool is elevated. Although this inverse relationship between the blood and fecal levels of radioactivity is present in most instances of occult steatorrhea, some patients with slight to moderate elevations of fecal radioactivity will have low normal or even normal blood values. Therefore, the radioactive content of the stool would appear to be a more sensitive and reliable index of steatorrhea than are the blood levels.

In many institutions, great difficulty may be experienced in collecting total 48-to-72-hour stool specimens, which must be free of urinary contamination. On the contrary, collection and analysis of blood samples at the fourth, fifth, and sixth hours after ingestion of the test meal is relatively simple and usually furnishes valuable information concerning the presence or absence of malabsorption within a matter of hours after beginning the test. In our opinion, both blood and stool determinations should be made in every case, at least until their relative usefulness has been established in each laboratory.

Other Methods.—Other methods that have been used in the study of fat absorption are the vitamin A tolerance test,[6] the chylomicron count,[7] serum carotene determination,[8] and serum turbidity measurement.[9] These tests are based on the absorption of fat-soluble substances and their demonstration in the serum or plasma after a test meal. They are influenced by such factors as lymph and blood flow as well as by lipid utilization. They provide indirect evidence of steatorrhea only and are of limited usefulness.

Nature and Cause of Steatorrhea

Significance.—It is generally accepted that frank steatorrhea is indicative of serious organic disease, yet the presence of occult steatorrhea is often overlooked or its importance unappreciated. As pointed out previously, most patients who have impairment of fat absorption will have either grossly normal stools or else diarrhea quite similar to that seen in patients with the irritable colon syndrome. The demonstration of an abnormal amount of fat in the stool is highly significant and requires careful study to determine the cause.

Clinical Picture.—Although one must turn to the laboratory to establish the presence of steatorrhea in many patients, a careful history and physical examination often will suggest that the patient is passing an excessive amount of fat in the stool. The most constant effect of this is loss of body weight, which is universally present in varying degrees. With this in mind, an unexplained weight loss should always make one suspicious of the presence of steatorrhea. Whatever the underlying condition may be that results in impaired absorption of fat, absorption of carbohydrates, proteins, vitamins, and minerals also may be impaired. As a result, one frequently finds secondary vitamin deficiencies, especially those related to the fat-soluble vitamins. Osteomalacia, with an associated reduction of serum calcium and phosphorus, due primarily to a vitamin D deficiency, is often found in frank steatorrhea. Ecchymotic areas or bleeding from the mucous membranes due to a deficiency of vitamin K are seen occasionally. Glossitis, stomatitis, and peripheral neuritis resulting from a B-complex vitamin deficiency once were common in patients with frank steatorrhea but now are relatively rare. Dependent edema resulting from a lowered serum albumin level is often present in patients with advanced cases, and anemia of varying degrees due to impaired absorption of iron and other hematopoietic factors is to be expected.

Distinction Between Digestive and Absorptive Malfunction.—An excessive amount of exogenous fat in the stool may result from one of two causes; (1) the failure to be digested properly or (2) failure, if digested, to be absorbed in the normal manner. Since the fundamental approach to therapy depends on whether the steatorrhea is due to lack of digestion or impairment of absorption, distinction between these two conditions is of practical importance. Within recent years the use of I^{131}-tagged lipids has proved of considerable value in solving this problem. This differentiation may be made with use of I^{131}-tagged triolein followed by I^{131}-tagged oleic acid in the same patient.[10] When absorption is impaired, both blood curves will be flat, with elevated radioactive content of the stools. If the error is one of digestion, only the triolein author that the exigencies of the military are such as to constitute an exception. The Council also believes that supplementary doses of vitamin A given to persons receiving diets low in fat should not be significantly greater than the recommended dietary allowance, which is 5,000 I.U. daily. The author indicated that the large doses of vitamin A given to older persons on a very low-fat diet are administered under medical surveillance and that no toxic symptoms have been observed.

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STEATORRHEA IN ADULTS

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The term steatorrhea implies to most physicians a diarrhea characterized by the passage of soft or watery, pale, frothy, greasy, voluminous, foul-smelling stools. However, the American Medical Dictionary defines steatorrhea as "the presence of an excess of fat in the stool." By this definition the passage of stools containing more fat than is found normally, but not having the physical properties described above, would be classified as steatorrhea. Thus, the term steatorrhea should embrace not only frank steatorrhea with the characteristic stool but also what may be called occult steatorrhea, in which an abnormal amount of fat is present although not readily apparent. Indeed, in our experience, occult steatorrhea is far more common than frank steatorrhea. It would be an error, therefore, to assume that an excessive amount of fat in the stool necessarily produces diarrhea, or, if actually present, that this diarrhea is steatorrhea in the sense that it is generally thought to be. Consequently, impairment of fat absorption is not suspected in many patients merely because either diarrhea is not present or the stool does not have the gross appearance usually associated with frank steatorrhea.

Methods of Demonstration

Inspection.—When steatorrhea is marked, inspection of the stool is all that is necessary to detect its presence. Unfortunately, in many if not in most cases an abnormal amount of fat in the stool cannot be determined by inspection alone.

Microscopic Examination.—The method of determining fat by microscopic examination is quite simple, consisting of staining the fat in the stool with a suitable reagent. However, this stains only neutral fat and certain forms of fatty acids. Soaps are not stained, and unless the stool is acidified and heated to convert the fat to globules, the demonstration of fat is missed frequently. Since there is little fat in the stool of the normal person, the presence of an appreciable amount of stained globules is conclusive evidence of steatorrhea, provided that mineral oil, which also stains in the same fashion, can be excluded. At best, this method permits a rough estimate of the degree of steatorrhea and is of limited usefulness, but it should always be employed as a screening procedure.

Fat Balance Study.—A far more reliable method and one conventionally used is the fat balance study. However, chemical determination of the fecal fat is time-consuming and laborious, requiring a metabolic ward and five to six days or even longer for

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ing fat (25 cc. of peanut oil) was ingested 30 minutes before the test, the absorption of triolein reverted to normal.[17] The clinical application of this principle, namely, ingestion of a small amount of fat 30 minutes before mealtime to stimulate the secretion of pancreatic enzymes and the flow of bile, has yielded promising results to date, but too few data are available to draw definite conclusions about the usefulness of this form of therapy.

Steatorrhea Due to Impairment of Absorption

Sprue.—At one time, it was generally agreed that there was no distinction between tropical and nontropical sprue.[12] However, recent studies have shown that they may differ in at least one important respect, namely, in their response to therapy.[18]

The preferred treatment in nontropical sprue is the gluten-free diet.[19] Although most patients respond promptly within a few days or weeks, the diet should be continued for at least three months. It is probable that failure to improve after this form of therapy means either lack of strict adherence to the diet or a mistaken diagnosis.[20] Macrocytic anemia, with associated malabsorption of radiocobalt (Co^{60})-labeled vitamin B_{12}, uncorrected by the administration of intrinsic factor, occurs fairly commonly in patients with nontropical sprue.[21] Nevertheless, in our experience, it has been unnecessary to supplement dietary treatment with folic acid, vitamin B_{12}, liver extract, or minerals. Six patients have been following this diet from one to five years, with a complete and sustained clinical, biochemical, hematological, and roentgenographically evident remission.[22] Furthermore, results of their absorption tests with the I^{131}-tagged lipids have reverted partially or completely to normal.[22] Microscopic sections of the mucosa of the upper small intestine of patients in relapse obtained by the intestinal biopsy tube have shown decreased numbers of villi, which are flattened, clubbed, and atrophic.[23]

Recent studies would indicate that patients with tropical sprue do not respond to the gluten-free diet but usually will recover after the use of folic acid, liver extract, or vitamin B_{12}.[24] Other observers have found that antibiotics are beneficial.[18] The intestinal mucosa shows essentially the same changes as noted in patients with nontropical sprue, and just why there should be a difference in response to therapy is not clear.

Intestinal Lipodystrophy.—Intestinal lipodystrophy is an interesting disease which probably is more common than is generally appreciated. There have been 10 known cases at Duke Hospital within the past 22 years and doubtless there are many more than the reported 90 to 100 cases in the world literature. At one time, the prognosis was considered hopeless and little was done other than to institute general supportive measures. We now have three patients who are alive and well 30 to 52 months after the diagnosis was made. On reviewing the therapy of these 10 patients the only form of treatment that was common to the survivors was antibiotics. Two patients received penicillin and streptomycin in large doses, one in combination with chlortetracycline and the other with neomycin. The third patient was given neomycin and tetracycline. Such an observation proves nothing, of course, but furnishes food for thought. We should take the position that intestinal lipodystrophy is not necessarily fatal and that if the patient can be tided over a critical period of malnutrition, recovery may take place.

Regional Enteritis.—Recent studies would indicate that most fat is absorbed in the upper portion of the small intestine.[25] Therefore, steatorrhea may not develop if only the terminal ileum is involved in a patient with regional enteritis. When it is present, we have found steroids distinctly beneficial, with the absorption of I^{131}-tagged lipids returning to normal along with clinical improvement. The gluten-free diet in these cases has had no appreciable effect. Resection of a large portion of the small intestine will necessarily result in steatorrhea for which there is no specific therapy.

Other Diseases.—Steatorrhea in patients with lymphoma or tuberculosis of the mesenteric glands is merely a symptom and requires no special therapy. All that one can do is to treat the underlying disease. Injury to the small intestine after radiation therapy for intra-abdominal malignancy probably will be seen more frequently and may result in steatorrhea. One has little to offer in the management of this condition other than symptomatic treatment.

Summary

Steatorrhea is a symptom, not a disease. It is often unsuspected because the characteristic stool is not present, and yet occult steatorrhea is common and indicative of serious organic disease. The radioiodine (I^{131})-tagged triolein test is probably the one most useful in demonstrating the presence of this type of steatorrhea. Frank steatorrhea, on the contrary, is readily demonstrable by inspection or microscopic examination of the stool. The distinction between digestive and absorptive malfunction is important and can be readily accomplished by the use of I^{131}-tagged lipids. Proper treatment of steatorrhea is highly gratifying in most cases.

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curve will be flat, with a corresponding elevation of fecal fat, whereas the blood and fecal values of oleic acid will be relatively normal.

Conditions Causing Steatorrhea.—It is beyond the scope of this communication to enter into a discussion of the differential diagnosis of disorders which may result in steatorrhea. Some of these are classified in the table, however. The reader is referred to recent excellent reviews of this subject.[11]

Treatment

General Principles.—Since weight loss is universally present in patients with steatorrhea, every effort should be made to increase their daily caloric intake. The diet should be high in proteins, with carbohydrates and fats as tolerated. Thus, a standard diet to be prescribed for all persons is unwise, since the fat and carbohydrate contents will necessarily be varied to suit the individual patient. Because multiple vitamin deficiencies are common, supplemental vitamin therapy is definitely indicated, with special emphasis on vitamins D and K. Iron and calcium, given either orally or parenterally, may be required in certain patients, and other hematopoietic factors, B_{12} and folic acid, are advisable in patients with macrocytic anemia. Many patients with diarrhea will develop a potassium deficit. Therefore, serum potassium levels should be followed closely and potassium administered when needed.

Convenient Working Classification of the More Important Conditions Which May Result in Steatorrhea

- Steatorrhea Due to a Defect of Digestion
  - Diseases of the pancreas
    - Chronic relapsing pancreatitis
    - Carcinoma
  - Diseases of the liver or biliary system
    - Advanced disease of the liver
    - Common duct obstruction
  - After surgical procedures
    - Gastric resection, partial or total, with or without vagotomy
    - Gastroenterostomy, with or without vagotomy
    - Gastroileostomy
- Steatorrhea Due to Impairment of Absorption
  - Diseases of the small intestine
    - Sprue
      - tropical
      - nontropical
    - Intestinal lipodystrophy (Whipple's disease)
    - Lymphoma
    - Regional enteritis
    - Tuberculosis of mesenteric glands
  - Resection of more than 50% of the small intestine
  - Radiation therapy

However, steatorrhea is a symptom and not a disease; therefore, to treat it without due regard for the underlying disorder is likely to yield discouraging results. The old concept of prescribing a high-protein, high-carbohydrate, low-fat diet[12] merely because there is an excessive amount of fat in the stool has been replaced by a more intelligent approach to the problem, based on its etiology.

Steatorrhea Due to Defect of Digestion

There are three major groups of patients who may develop steatorrhea due to defects of digestion.

Diseases of the Pancreas.—The first such group is that of patients with pancreatic disease.

Chronic Relapsing Pancreatitis: In patients who have had chronic relapsing pancreatitis over a long period of time, the pancreas is gradually destroyed and insufficiency of pancreatic enzymes results. Dietary treatment in these cases has proved disappointing. It is true that restriction of fat will decrease the steatorrhea to some extent, but a more successful approach would be an effort to correct the digestive deficiency. Replacement therapy in the form of pancreatic enzymes obviously is indicated. A pancreatic extract in doses of from 9 to 12 Gm. per day has been tried with encouraging results.[13] A significant increase in absorption with use of I^{131}-tagged triolein has been noted along with clinical improvement.

Carcinoma of the Pancreas: Most patients with carcinoma of the pancreas will have steatorrhea. However, this is rarely troublesome and requires no specific treatment.

Disease of the Liver and Biliary System.—Many patients with advanced liver disease will have distressing diarrhea, usually occult steatorrhea. Treatment of the diarrhea in these cases has been of little value, and all that one can do is to treat the underlying disease. The steatorrhea that may accompany biliary tract obstruction requires no treatment per se, since it disappears once the obstruction has been relieved.

Steatorrhea After Surgical Procedures.—About 50% of all patients who have a subtotal gastric resection (Billroth 2) or a gastroenterostomy with or without vagotomy will have steatorrhea. With use of I^{131}-tagged lipids it was found that triolein was poorly absorbed, but the absorption of oleic acid was normal, in most cases.[14] This tends to confirm the belief that the steatorrhea that develops in this group of patients is primarily a defect of digestion rather than an error of absorption.[15] The work of Lundh[16] adds additional support to this hypothesis. He has shown that the pancreas is capable of secreting normally after gastric resection, but mixing of a test meal and digestive juices was not observed within the lumen of the entire small intestine.

Replacement therapy, with both pancreatic enzymes and bile salts, has been disappointing. Recent observations point to a possible answer to the problem of therapy in these cases. As noted above, many patients who have had a gastric resection will have a marked impairment of absorption of triolein. It was found that if a meal contain-

CYSTIC FIBROSIS OF THE PANCREAS

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It is generally recognized that the term "celiac syndrome" includes several pediatric disease entities which give rise to malnutrition, abnormal stools with steatorrhea, and multiple vitamin deficiencies. Of these various disorders the most important are idiopathic celiac disease and cystic fibrosis of the pancreas.

Celiac disease in children has become increasingly rare in this country in the last few years because of better knowledge of nutritional requirements and the advent of antibiotic agents, which prevent the chronic infections that used to act as trigger mechanisms in initiating the clinical manifestations. In contrast, because of the introduction of effective antibacterial drugs and better dietary control, the life span of patients with cystic fibrosis has increased greatly. In former years these patients died in infancy or early childhood of bronchopneumonia or occasionally of severe malnutrition. At the present time, fibrocystic patients are observed with increasing frequency, not only in the pediatric age group but among adolescents and young adults. Cystic fibrosis, therefore, presents an increasing challenge to the medical profession.

Cystic fibrosis of the pancreas is a generalized hereditary disease of children, adolescents, and young adults in whom there is a dysfunction of the exocrine glands. In the fully manifested syndrome there is chronic pulmonary disease, pancreatic deficiency, abnormally high sweat electrolyte levels, and at times cirrhosis of the liver. Gradation in or absence of involvement of the organs or glandular systems usually affected leads to many variations in the clinical picture.

The nature of this widespread disturbance of exocrine secretion is not known as yet. The basic defect appears to be genetically transmitted, probably as a recessive trait. Evidence is accumulating which indicates that persons who are homozygotic for the gene of cystic fibrosis show the full disease picture, while heterozygotic persons exhibit either no detectable change or only some manifestation of the disorder, usually abnormally high sweat electrolyte levels.

In 1936, Fanconi and others[1] described three cases of cystic fibrosis, but the disease was neither widely recognized as a separate entity nor clinically diagnosed until 1938 when three series of postmortem cases were reported independently by Andersen,[2] Blackfan and May,[3] and Harper.[4]

Cystic fibrosis occurs equally and without regard to sex in Caucasoid persons. It is rarely found in Negro and has never been reported in Mongoloid patients. The incidence of patients with the fully manifested disease (homozygotes) is estimated as 1 per 1,000 live births and that of heterozygotes as 2 to 20% of the population. At Babies' Hospital within the past 20 years, 550 cases of cystic fibrosis have been observed, most of these cases occurring in the last 10 years.

Non-mucus-producing exocrine glands, such as the sweat, parotid, and tear glands, show no pathological changes even though their secretions are abnormal in chemical composition. Mucus-secreting exocrine glands throughout the body may present an accumulation of abnormal secretions leading to dilatation of the secretory organ itself. The most striking pathological manifestations are found in the pancreas of patients in whom this organ is involved. These manifestations attracted the attention of the early investigators and gave the disease its name. In the pancreas, amorphous eosinophilic concretions obstruct the large and small ducts, with consequent dilatation of the acini and degeneration of the exocrine parenchyma, which is replaced by fibrous tissue and eventually by fat. The islands of Langerhans appear normal. Similar changes in the liver, due to obstruction of bile canaliculi by abnormal secretions, give rise to focal biliary fibrosis and, at times, to more extensive multilobular biliary cirrhosis. Bronchial obstruction by viscid secretions and the consequent generalized emphysema constitute the primary and cardinal manifestation of the pulmonary involvement in patients with cystic fibrosis, although changes due to severe and chronic infection dominate the pathological picture.

Involvement of Abdominal Organs

Meconium Ileus.—In about 10% of patients with cystic fibrosis, intestinal obstruction is present at birth (so-called meconium ileus). Putty-like, grayish meconium plugs the lumen of the small intestine, usually near the ileocecal valve. Unless corrected by surgical intervention the condition proves fatal. Patients who survive have the same course and outlook as do those who have not had meconium ileus.[5] The pathogenesis of meconium ileus has been related to pancreatic achylia occurring before birth,[6] but abnormal intestinal secretions may be a factor in its production.

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HAEMOLYTIC DISEASE OF THE NEW-BORN.—Haemolytic disease of the new-born is a condition afflicting the foetus or new-born animal which is brought about by maternal blood-group antibodies and is primarily manifested by an acute haemolytic anemia, often with jaundice. The condition in man has also been called erythroblastosis foetalis. It is encountered in . . . man, the horse and the pig. In the last species it is of relatively recent origin, but in man and the horse recognizable cases of the disease may be found in the literature of the seventeenth and eighteenth centuries. . . . In the mule-breeding areas of France, Italy and Spain the disease in mule foals (first called "pissement de sang" from the haemoglobinuria but later "l'ictère du poulain" from the jaundice) was the subject of comment from the time of Villa-Roja's account in 1774. Initially an understanding of the condition in foals made more rapid progress than an understanding of that in man, for as early as 1842 Carrère noted the familial tendency and ascribed the condition to the hybrid mating; and in 1861 Chicoli demonstrated that the foals were healthy at birth and could be reared successfully if fed on cow's milk for the first three days, after which they could safely be returned to the mare. All this was swept away by the mania for bacteriology that followed the work of Pasteur, and thereafter the search for a microbial agent, and its apparent discovery in 1924, wasted the years until 1947 when Caroli & Bessis showed that blood-group iso-immunization was the cause, six years after this point had been established for the human form of the disease. . . . Although many of the human blood-group substances inherited by the foetus from the father but lacking in the mother are capable of immunizing the mother, only the Rh antigen D and the blood-group substances A and B are of general consequence in the causation of haemolytic disease: possibly because D and A are more strongly antigenic than are other blood-group substances. —F. Roberts, M.D., Haemolytic Disease of the New-Born, *British Medical Bulletin*, May, 1959.

mally resist infection by this organism elsewhere in the body (e. g., the skin). Recent studies[14] have shown that no one bacteriophage type of staphylococcus is found in cystic fibrosis but that the distribution of types is that expected of in-hospital patients.

Sinusitis.—Involvement of the paranasal sinuses is a regular and expected finding on roentgenographic examination. Progressive pneumatization of the sinuses with age is responsible in part for clinical symptoms in later childhood and young adult life. A nasal voice, postnasal drip, and polyps, often necessitating surgical removal and recurring after some time, are frequently seen in such patients.

Complications of Severe Pulmonary Involvement.—Numerous complications arise in the course of severe pulmonary disease. Lobar atelectasis, with collapse of one or more lobes of the right lung, occurs in 5 to 10% of fibrocystic patients. It is rarely seen in the left lung. Cystic fibrosis[15] is one of the main causes of noncongenital lobar atelectasis during the first year of life. Small and multiple lung abscesses are common and usually respond to the antibiotic treatment which is administered for the pulmonary disease.

Sudden death from asphyxia, due to sudden flooding of the trachea with copious amounts of thick, tenacious bronchial secretions in a debilitated infant or small child, has been seen repeatedly. Spontaneous pneumothorax with mediastinal and subcutaneous emphysema was seen in six patients, and with one exception was not difficult to treat. However, it is a poor prognostic sign that implies serious and progressive lung involvement. The same can be said of hemoptysis, which we also observed in six instances. Both complications occurred in patients in the older age group.

Chronic cor pulmonale, with clinical and roentgenographic evidence of enlargement of the heart and pulmonary artery and cardiac embarrassment, has been present in a few patients with long-standing, severe, and progressive lung disease. Acute cor pulmonale, with dilatation of the heart as evidenced by roentgenography and the clinical signs of cardiac failure, frequently occurs during the attacks of sudden and severe bronchial obstruction due to sudden relapse in the pulmonary disease. If the patient survives and responds to antibiotic treatment, the heart returns to a normal size. Digitalis has been of invaluable help in treating both kinds of patients with cor pulmonale.

Electrolyte Disturbances in Cystic Fibrosis

Sweat Glands.—In 1953, it was shown in our clinic that the sweat electrolyte concentration was increased in 99% of patients with cystic fibrosis.[16] Despite normal renal and adrenal function such patients could not conserve salt in sweat under stress.[16] In hot weather, the massive loss of sodium chloride by this route led to cardiovascular collapse and at times to death, thus explaining the unusual sensitivity of fibrocystic patients to heat.[17] In subsequent years, these findings have been confirmed by many authors, whose work was reviewed by Vink[18] and by Barbero and Sibinga.[19] No other disease entity has been found that results in a rise in sweat electrolyte levels, with the exception of untreated adrenal insufficiency.

Fig. 1 shows past experience with the sweat test in this hospital. The mean for sweat chloride concentration in control patients, who represented a variety of pathological conditions, is 19 mEq. per liter and in patients with cystic fibrosis 102 mEq. per liter. In this laboratory, 50 mEq. per liter is taken as the dividing line between normal and abnormal; the overlap between the two groups is slight. Values for sweat sodium are practically the same as for chlorides. The actual figures vary slightly according to the technical methods used in different clinics.

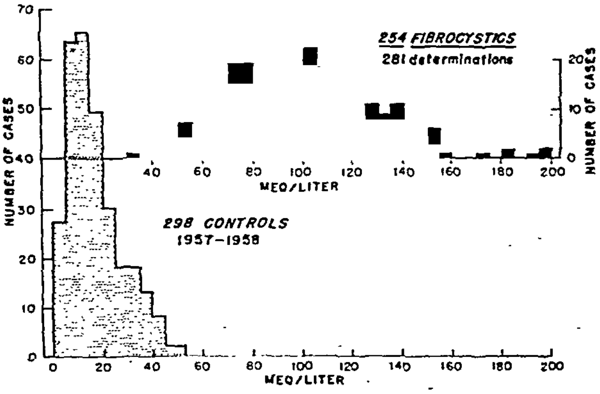

Fig. 1.—Chloride levels in sweat from trunk of patients with cystic fibrosis of pancreas and control patients.

Salivary and Tear Glands.—Similar changes in saliva were observed in our original studies[16] and by other authors[19] and more recently have been demonstrated in tears.[20] Electrolyte levels in these secretions were higher in fibrocystics than in the control patients.

Serum Electrolytes.—Serum electrolyte concentrations in patients with cystic fibrosis are normal when the patient is doing reasonably well clinically (see table). If severe pulmonary disease is present, especially in the early phases of an attack of widespread bronchial obstruction, there may be uncompensated respiratory acidosis, a low pH of the blood, elevated carbon dioxide-combining power, but normal serum chloride, sodium, and potassium levels. After compensation by excretion of chloride via the kidneys, a process that may take some time, the blood pH rises to normal values, carbon dioxide is still increased, but the chloride contents are decreased, at times markedly. The serum sodium and potassium levels remain normal. In the heat

Pancreatic Achylia.—Pancreatic insufficiency is present in about 80% of patients.[7] The absence of pancreatic trypsin, lipase, and amylase leads to poor digestion and absorption of foodstuffs. In contrast to fats, proteins are well tolerated, making possible the attainment of positive nitrogen balance through increased intake. The abdomen is distended and the stools, increased in number, are bulky, greasy, and extremely foul. Malnutrition may be marked despite an apparently adequate dietary intake. The presence of this combination is of diagnostic assistance. In patients with normal pancreatic function, symptoms may appear later or remain in abeyance indefinitely.

Large amounts of liposoluble vitamins are lost in the stools. At the present time, vitamin A deficiency does not cause concern. Rickets has never been seen in patients with cystic fibrosis, a fact which is not clearly explained. Vitamin K deficiency, leading to prolonged prothrombin time and bleeding, is occasionally observed. Gordon and Nitowsky[8] recently demonstrated that most children suffering from this disease have a deficiency of vitamin E and exhibit creatinuria that ceases on administration of this dietary supplement.

Recent studies[9] in which fats tagged with radio-iodine (I^{131}) were used show that fibrocystic patients do not absorb neutral fats or fatty acids normally. This peculiar behavior leads us to believe that pancreatic deficiency may not be the only factor in the malabsorption shown by patients with this disorder. Indeed, a mucoprotein, abnormal in its physicochemical properties and chemical structure, has been isolated from the duodenal contents of most patients with cystic fibrosis whether pancreatic achylia is present or not.[10] A comparable substance may be present in other parts of the intestinal tract.

Cirrhosis of the Liver with Portal Hypertension.—Most patients with cystic fibrosis on whom autopsy is performed have localized foci of biliary obstruction and fibrosis. With time, these changes become more extensive and may give rise to a distinctive type of multilobular biliary cirrhosis.[11] Through years of destruction and regeneration of the parenchyma, the hepatic architecture becomes distorted; portal hypertension arises; and ascites, hypersplenism, and gastrointestinal bleeding appear. Because of the focal nature of the process, results of liver function tests are frequently negative, and jaundice is absent or slight if present even at this advanced stage.

Other Abdominal Complications.—Repeated episodes of prolapse of the rectum occur most frequently in infants and young children with this disease[12] but have been observed in the older age group as well. The mechanism of the prolapse is not clear, but it disappears with improved dietary control. An operation never is necessary. Since cystic fibrosis is the commonest cause of prolapse of the rectum in the pediatric age group, its repeated occurrence in a patient known to have a ravenous appetite is suggestive of this disease.

Small, hard, nontender fecal masses frequently are found in the large intestine of fibrocystic patients, most often in the right lower quadrant. They may be an expression of the abnormal mucoids present in the intestinal secretions of these patients. Constipation, consequent on restricted diets, seems to be a factor in their genesis and should be avoided. Surgery is not necessary unless the fecal masses give rise to symptoms. However, it is important to differentiate these cases from appendiceal abscess which is masked by the continuous administration of antibiotics that obtains in most of these patients.

Abdominal pains, at times severe and of differing character, frequently are present in patients with cystic fibrosis. Cramps due to meteorism and loose bowel movements, muscular pains because of severe coughing, and a large tender liver as an expression of cardiac embarrassment are seen. Occasionally, however, the abdominal pains are unexplained. In at least one case, acute pancreatitis has been demonstrated. This condition may be more common than realized, especially in patients who are losing their pancreatic function. Perhaps a similar process occurred in two patients with calcification of the pancreas who eventually developed diabetes mellitus.

Involvement of the Respiratory Tract

Chronic Lung Disease.—Chronic pulmonary disease is present in almost all patients at some time in the course of their illness.[13] It frequently is severe and progressive and may appear weeks, months, or years after birth. For some time, the patient has a dry, nonproductive cough. Later, usually after an acute respiratory infection (frequently after measles or pertussis), the signs of generalized bronchial obstruction and secondary infection appear. At this stage, respiratory distress always is present to some degree. At times it is severe and the patient is quite ill. The infection may be brought under temporary control with antibiotic therapy, but some degree of bronchial obstruction usually persists. The cycle is then repeated on the occasion of subsequent respiratory infections. Any one episode may be fatal. If the bronchi are irreversibly damaged, the pulmonary disease is progressive and eventually leads to pulmonary insufficiency, resulting in death through various complications within an average of one to three years. If permanent damage has not been done to the bronchial wall, antibiotics in prophylactic dosage are effective in keeping the disease in check.

Hemolytic staphylococcus aureus is recovered on culture of the sputum or nasopharynx of most patients with cystic fibrosis. This constant association is the more striking, since fibrocystic patients nor-well cause irreversible precipitation of mucoproteins in such organs as the pancreas and the liver, thus initiating the chain of clinical events.

Unexplained as yet is the increase in parotid secretory rate found in fibrocystic patients.[27] This represents a third abnormality in exocrine secretion, in addition to the abnormal electrolyte levels of sweat, saliva, and tears and the abnormal structure of mucous secretions.

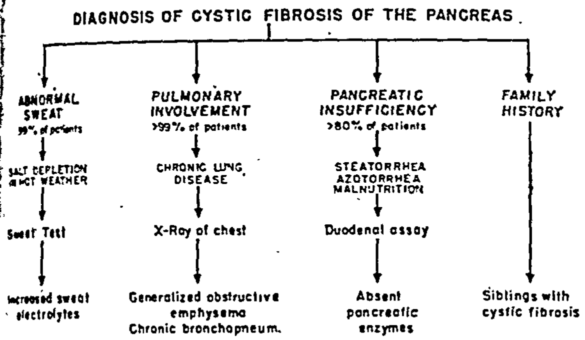

Fig. 2.—Criteria for diagnosis of cystic fibrosis of pancreas.

Diagnosis

Diagnosis of cystic fibrosis should be based on the four criteria listed in fig. 2, (1) increase in electrolyte concentration of sweat; (2) absence of pancreatic enzymes on assay of aspirated duodenal secretions; (3) chronic pulmonary involvement; and (4) family history of the disorder. It is important to realize that one or more of these criteria may be absent in the individual patient; however, two criteria are usually sufficient for diagnosis.

The sweat test, as originally described and developed,[16] but with some changes in the procedure, generally is accepted [28] as the simplest and most reliable test. It usually is sufficient for diagnosis of this disease, in addition to the clinical picture. This test is not dependent on pancreatic function and, therefore, will give a positive result even in patients in whom the pancreas is not involved. A level of more than 60 mEq. per liter of sweat chloride is diagnostic of cystic fibrosis, and values between 50 and 60 mEq. per liter are highly suggestive of this disease. Values for sweat sodium contents are similar.

Drainage for determination of tryptic activity of duodenal contents may be performed as a confirmatory test and to evaluate pancreatic function. Other investigations [5a] also based on pancreatic function are less reliable. Testing the stools for tryptic activity gives many false-positive and false-negative results.

In our clinic, the sweat test is performed quantitatively with use of the plastic bag introduced by Shwachman and co-workers [13a] to make patients perspire. The sweat is collected in two patches of gauze in the scapular region and analyzed for its content of chloride or sodium or both, as originally described.[16] Recently, Gibson and Cooke [29] obtained sweat for analysis through stimulation of the glands by iontophoresis of a cholinergic substance. This eventually may prove to be the most satisfactory method of performing the sweat test.

Several ways of qualitatively estimating sweat chloride in simple fashion have been described.[30] All are based on similar principles and require use of similar materials. If performed properly, they are satisfactory as screening procedures. It should be stressed that the diagnosis of cystic fibrosis is of such importance to the patient and to the family, because of its prognostic and genetic implications, that an accurate quantitative sweat test should be performed in all suspected cases and evaluated in the light of the other clinical features.

In the pediatric age group, the presence of generalized chronic obstructive emphysema as observed in physical examination and on roentgenograms of the chest, while not pathognomonic, is highly suggestive of cystic fibrosis (fig. 3). It invariably is found in fibrocystic patients when pulmonary involvement is present. Children with chronic lung disease, but without signs of generalized chronic bronchial obstruction, have other disease entities.

Therapy and Prognosis

Therapy of chronic lung disease with antibiotic agents deserves major emphasis, since pulmonary involvement dominates the clinical picture and determines the fate of the patient.

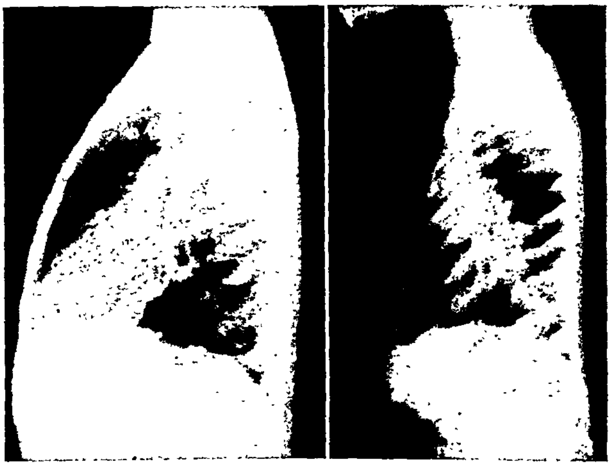

Fig. 3.—*Left,* lateral roentgenogram of chest of 6½-year-old girl with cystic fibrosis. *Right,* lateral roentgenogram of chest of 7-year-old girl with other chronic lung disease. Note markedly increased anteroposterior thoracic diameter in patient at left due to obstructive emphysema and contrast with that of patient at right.

In an effort to dominate the infection in the more severe cases, an intensive course of treatment is given for 7 to 15 days. This includes the intramuscular administration of penicillin (1 million casualties, because of the massive outpouring of electrolytes in sweat, the concentrations of serum electrolytes decrease, with the exception of potassium.[18]

The question frequently arises in summer months whether a patient with cystic fibrosis and chronic respiratory disease is in poor condition because of his lung involvement or because of the loss of salt through sweat. A determination of serum sodium (not chloride) concentration quickly will give the answer. If excessive salt has been lost through sweat, the serum sodium level will be low. If serum values for this electrolyte are within normal limits, the patient's poor condition cannot be attributed to this mechanism.

Recently, we observed five infants with cystic fibrosis, extreme hypoelectrolytemia, and at times with metabolic alkalosis. These infants were observed during the winter months and under circumstances not easily explained by loss of salt through sweat. Frequently, such infants are labeled erroneously as having adrenal insufficiency, from which fibrocystic disease in this age group, therefore, must be differentiated.

Serum Electrolyte Patterns in Patients with Cystic Fibrosis of Pancreas

Clinical Condition		Serum*: pH	Carbon Dioxide	Chloride	Sodium	Potassium	Electrolyte Pattern	
Doing Well		N	N	N	N	N	Normal	
Pulmonary Disease	Acute relapse	Acid	Increase	N	N	N	Not compensated	Respiratory Acidosis
	Chronic	N	Increase	Decrease	N	N	Compensated	
Heat Casualties (Acute salt loss)		N	Decrease	Decrease	Decrease	N	Hypoelectrolytemia	

* N = normal.

Pathogenesis and Genetics

After recognition of the consistent involvement of non-mucus-producing glands (sweat, parotid, and tear glands),[16] as well as of mucus-secreting ones, it became evident that despite its name, cystic fibrosis is a generalized disturbance of exocrine function.[21] It is not primarily a disease of the pancreas but one in which this organ is frequently, but not necessarily, involved. The basic defect in cystic fibrosis is unknown. Speculation has followed various channels, but there is general agreement that whatever its nature it is genetically transmitted, probably as a recessive trait. According to this hypothesis, homozygotes should have all or most of the clinical manifestations. Gochberg and Cooke[22] have postulated that an inherited deficiency of some enzyme, coenzyme, or substrate, with consequent alteration in the release of energy, may be responsible for the secretory defect of the exocrine glands.

From 20 to 30% of immediate relatives (both children and adults) of patients with fibrocystic disease have sweat electrolyte levels elevated above normal values;[23] a smaller number also may have some degree of pulmonary involvement. Recent investigations[24] suggest that some children diagnosed as having bronchial asthma and some adults with chronic generalized obstructive emphysema in reality may have partially expressed forms of cystic fibrosis. These studies suggest that the heterozygous state may give rise to clinical manifestations more often than previously suspected. In several genetic studies[25] it has been calculated that from 2 to 20% of the population must carry the recessive gene, a surprisingly high figure. Hsia[25a] pointed out that since persons homozygotic for cystic fibrosis usually die before reproducing and since there is no evidence that heterozygotic persons have greater survival value or reproduction fitness than the general population, it must be assumed that an unusually high mutation rate assures persistence of the recessive gene in the population.

Recently, one of us (P. A. S.)[7a] found that sweat electrolytes of homozygotic persons behave fundamentally differently from those of heterozygotic persons. To determine this, we simultaneously restricted salt in the diet and administered either desoxycorticosterone acetate or 9-alpha-fluorohydrocortisone, which is known to decrease sweat electrolyte concentrations in normal persons. Heterozygotes are able to conserve salt in sweat under stress in the same way that healthy persons do, and they can bring their sweat electrolyte levels down to normal values. Homozygotes cannot conserve salt in sweat and thus are unusually susceptible to hot weather. These findings lead us to speculate that the basic defect responsible for the widespread exocrine gland dysfunction may be present in varying degrees, as occurs in other disease conditions (e. g., sickle cell anemia). This might offer one explanation of the variability in the severity and in the manifestations of this disease.

It was mentioned that in the duodenal contents of most fibrocystic patients a mucoprotein is found which is easily denatured and rendered insoluble.[10] The chemical structure of this mucoprotein has certain peculiarities, especially in its content and distribution of sialic acid and fucose.[26] If a similar abnormal composition of mucoids is present in secretions throughout the body, the resulting changes in the physiochemical environment might electrolytes, and at times cirrhosis of the liver. Cystic fibrosis is a hereditary disease, thought to be transmitted as a recessive trait. The basic defect is not known as yet. It occurs in Caucasoid, is rare in Negro, and has never been described in Mongoloid patients. In the fully manifested form (homozygotic), it occurs in 1 out of 1,000 live births, and as many as 20% of the population are thought to carry the recessive trait (heterozygotic). Virtually all cases of pancreatic deficiency in the pediatric age group and the great majority of children with chronic (nontuberculous) pulmonary disease in this country are due to this disorder. The diagnosis of fibrocystic disease is based primarily on the finding of an abnormally high concentration of sweat chlorides and sodium.

The prognosis of patients with cystic fibrosis depends on the severity of the lung involvement. Treatment of the pulmonary disease with antibiotic agents deserves the major emphasis. While less important to the ultimate outlook, attention should be paid to the effects of nutritional disturbances. The malabsorption seen in many patients with cystic fibrosis usually can be offset by moderate restriction of the fat intake and the addition of pancreatic extracts to the diet. Additional salt is needed in summer. Meconium ileus and portal hypertension due to cirrhosis of the liver require surgical treatment. Massive salt depletion in hot weather may present a real medical emergency.

Five hundred fifty patients with cystic fibrosis have been observed at Babies Hospital in New York since 1939, the great majority in the last 10 years. The mortality has been high and due mostly to the chronic progressive pulmonary involvement. Of the total 106 patients have survived beyond the age of 10 years, the oldest to the age of 24 years. Fibrocystic disease in young adults is briefly described as it differs in some of its features from that seen in infancy.

Addendum

Since this paper was submitted, Koch and associates[33] in Germany, in a series of elaborate studies, have pointed to the possible relation of cystic fibrosis to some chronic pulmonary and gastrointestinal disorders of adults. According to these authors, fibrocystic disease may prove even commoner in adults than in children.

National Institutes of Health, Bethesda 14, Md. (Dr. di Sant'Agnese).

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units per 24 hours) and, at times, streptomycin (40 mg. per kilogram of body weight or 1 Gm. per day). One of the broad-spectrum antibiotic agents (tetracycline, chloramphenicol, erythromycin, or novobiocin) is given orally (50 mg. per kilogram of body weight per 24 hours for children). The combination of penicillin (200,000 units) and streptomycin (200 mg.) is given by inhalation four or five times a day. More recently, neomycin (250 mg.) and polymixin (10 mg.) have been used with success when given by inhalation four times per day. Administration by inhalation is useful as a therapeutic rather than a prophylactic maneuver and requires an air compressor. Two milliliters of a saline solution containing the prescribed amounts of antibiotics should be added together in a nebulizer and nebulized with compressed air flowing at 5 to 6 liters per minute.

If clinical and roentgenographic signs of pulmonary involvement persist, continued administration of antimicrobial agents is indicated. A broad-spectrum antibiotic, 10 to 20 mg. per kilogram of body weight per 24 hours, generally is satisfactory. The choice of drug to be used will be based on bacterial sensitivities.

Kanamycin, given by intramuscular injection, has been ineffective at times but has been used to advantage in a smaller number of cases. Because of potential toxicity and difficulty of administration, this and other agents (ristocetin, vancomycin) should be reserved for patients from whom Staphylococcus aureus that is sensitive to these drugs has been isolated, and for patients who have not responded satisfactorily to treatment with other antibiotics.

Pulmonary surgery rarely is indicated, since the pulmonary disease is usually bilateral and generalized. Out of a total of more than 1,200 patients seen at Babies' Hospital in New York and the Children's Medical Center in Boston,[31] only 16 have been subjected to lobectomy. Aerosols of propylene glycol and saline, postural drainage, and other physical methods are of assistance in the more severe cases. Inhalation of enzymatic preparations generally has been ineffective. Therapeutic bronchoscopy is to be avoided in the younger age group because of adverse reactions to this procedure and its failure to yield lasting results. No specific treatment directed to the paranasal sinuses usually is needed. It is part of the respiratory involvement in cystic fibrosis and responds best to the antibiotic treatment administered for the pulmonary disease.

The effects of pancreatic deficiency, when present, are less important than those of pulmonary disease for the ultimate outlook of the patient. There is no evidence that they exert any direct effect on the respiratory involvement. The malabsorption seen in many patients with cystic fibrosis usually can be offset by a large intake of food, with moderate restriction of the fat intake and addition of pancreatic extracts to the diet. Additional salt is needed in summer. However, the need for dietary restriction varies greatly among patients with pancreatic achylia. The nutritional state, even in the latter group, is more closely correlated with the severity of the pulmonary disease than with pancreatic function.

Meconium ileus and portal hypertension due to cirrhosis of the liver require surgical treatment. Massive salt depletion in hot weather may present a real medical emergency. Intravenous infusions of isotonic sodium chloride solution are needed urgently to reconstitute an adequate extracellular fluid volume and to avoid cardiovascular collapse.

Of the 550 patients with cystic fibrosis seen at Babies' Hospital, more than 300 are dead. Of the total, 106 survived beyond the age of 10 years, the oldest to the age of 24 years; of these 85 are now living. More than 90% of the deaths were due to progressive chronic pulmonary disease.

Cystic Fibrosis in Young Adults

A word should be said about adolescents an young adults with cystic fibrosis, since the diseas differs somewhat in its manifestations in this ag group from that seen in infancy. As a group, th older patients are doing better than the young ones, perhaps because they would not have surviv to a fairly old age unless the respiratory manifest tions had been relatively mild, although at lea some degree of chronic pulmonary disease is pre ent in virtually all patients. Sinusitis with its co plications, notably polyps, has been a serious pro lem in this age group. Although nearly all ha pancreatic deficiency, digestive symptoms are f quently minimal, and most patients tolerate a v tually unrestricted diet. Digestion and absorption of food seems more efficient with advancing age because the ravenous appetite of young children decreases toward much more normal levels in the older age group. Growth, so characteristically retarded in most of the younger children, eventually seems to proceed more normally. Although growth is delayed, these patients usually reach low normal values in height. Sexual maturation proceeds normally, although at times it is delayed somewhat. Finally, the psychological effects of chronic illness and of limitations in physical activity have dominated the course of a few patients.[32]

Summary

Cystic fibrosis of the pancreas was recognized as a separate disease entity in 1938. It is now observed with increasing frequency in children, adolescents, and young adults. Despite its name, cystic fibrosis is now recognized as a generalized disturbance in the function of exocrine glands. In the fully manifested form, there is chronic pulmonary disease, pancreatic deficiency, abnormally high levels of sweat voir, will limit the amount of food taken at any one time, either mechanically or by production of a disagreeable feeling of fulness. If it does not act as a reservoir, or if there is no gastric remnant, the possibility of developing debilitating signs and symptoms is even greater, since sudden introduction of potentially hypertonic foodstuffs into the jejunum is a prerequisite for the production of the "dumping syndrome." Other less common but important sequelae to gastrectomy are the "afferent loop syndrome," in which a partial mechanical obstruction limits the flow of pancreatic, biliary, and duodenal juices; postprandial regurgitation of bile; and postprandial hypoglycemia.

While few patients subjected to gastrectomy would be expected to have all of the symptoms mentioned above, any one symptom might prejudice them against the ingestion of food. It is primarily this failure to ingest adequate calories that prevents most patients from regaining normal weight.

The Dumping Syndrome

Perhaps the most common and distressing symptoms that follow gastrectomy are those associated with the dumping syndrome, which is a series of signs and symptoms experienced within 15 to 20 minutes after the ingestion of food. They consist of the sensation of epigastric fulness, distention, increased intestinal motility, and occasionally diarrhea. Accompanying these gastrointestinal symptoms may be weakness, pallor, sweating, tachycardia, changes in blood pressure (generally hypotension) and even precordial pain. Patients are frequently relieved of their symptoms by lying down. Vasomotor and cardiac symptoms may be prevented by the rapid intravenous infusion of plasma expanders immediately after eating. These symptoms generally disappear within three-quarters of an hour. This syndrome should not be confused with the hypoglycemia which occurs in some gastrectomized patients several hours after eating.

The etiology of the dumping syndrome has been the subject of considerable speculation. Machella[4] noted that ingestion of hypertonic glucose, hypertonic protein hydrolysate, and hypertonic sodium sulfate would produce signs and symptoms of the dumping syndrome in gastrectomized patients and that similar dumping episodes could be produced in patients without gastrectomy when these solutions were introduced into the jejunum by tube. He concluded that jejunal distention, with a consequent sympathetic response, accounted for symptoms of the dumping syndrome, since distention might be expected as hypertonic solutions became diluted by the rapid inflow of intestinal juices. He also noted that distention of the jejunum with a balloon occasionally caused similar symptoms. With use of hypertonic glucose or hypertonic saline as a test meal, Roberts and co-workers[5] confirmed these clinical findings and also defined the following physiological responses: an increase in hematocrit value, a sharp drop in plasma volume of from 300 to 700 cc., and (in gastrectomized dogs) a significant drop in cardiac output. Simultaneous electrocardiographic changes take place which, although nonspecific, are compatible with either myocardial ischemia or sympathetic stimulation. The changes in hematocrit value, blood volume, and electrocardiogram are summarized in fig. 1, which also includes determinations of plasma sodium, potassium, and phosphate levels. The changes in hematocrit value, blood volume, and electrocardiogram occur at the time when symptoms are present; whereas a decrease in potassium and phosphate occurs later. Since changes in potassium and phosphate occur late, and only after administration of glucose or starch (not hypertonic sodium chloride solution), it seems unlikely that these electrolyte shifts are of etiological significance in the dumping syndrome.

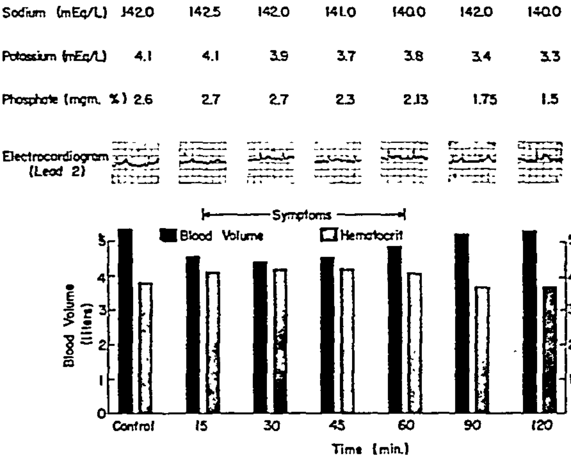

Fig. 1.—Changes in hematocrit value, blood volume, electrocardiogram, and electrolyte levels in patients with dumping syndrome. (Reprinted, with permission, from the *New York State Journal of Medicine* 55:2897 [Oct. 15] 1955.)

Quantitatively, it has been found that nutrients differ in their ability to cause the dumping syndrome and to produce changes in blood volume.[3] Thus, sufficient quantities of hypertonic solutions, introduced into the jejunum, will almost invariably cause the dumping syndrome. Proteins, such as steak or chopped meat, rarely produce sufficient change in blood volume to cause symptoms. In the usual diet, carbohydrate is the chief offender and finely emulsified fat next, with fat in normal form and protein causing the least distress.

More recently, Lawrence and associates[6] demonstrated a marked decrease in pancreatic flow when hypertonic sodium chloride solution or glucose was introduced into the jejunum of dogs. This decrease in flow also can be prevented by the simultaneous administration of plasma expanders. While this observation does not account for the symptoms of the dumping syndrome, it may be of importance in explaining the malabsorption frequently seen after gastrectomy.

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NUTRITION AFTER GASTRIC RESECTION

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Nutritional impairment often occurs after gastrectomy. In a recent review article, Randall[1] estimated that about one-half of all patients subjected to subtotal gastrectomy have sufficient nutritional problems to prevent their regaining normal preoperative weight, and from 2 to 10% are severely disabled as a result of their operation. With total gastrectomy, at least two-thirds of the patients have nutritional problems, one-third of which are severe. Few such patients regain their preoperative weight.

Nutritional impairment after gastrectomy implies either inadequate intake of food, malabsorption of ingested food, increased metabolic requirements, or a combination of all of these factors. The object of this discussion is to evaluate each of these factors in order to present a more comprehensive program for care of the nutritionally disabled patient after gastrectomy.

Inadequate Intake of Food

There is evidence that gastrectomized patients eat far less than they did prior to surgery. In a study of 35 patients who underwent subtotal gastrectomy, MacLean and co-workers[2] estimated a 20 to 35% decrease in oral intake after operation. In a careful dietary analysis of 40 symptomatic patients subjected to subtotal gastrectomy and 20 patients subjected to total gastrectomy, Roberts and associates[3] found that most patients had an intake of less than 1,800 calories per day and only eight ingested more than 2,200 calories per day. It is necessary to take an actual dietary history to obtain evidence of inadequate intake, since the average patient gives an inaccurate history of intake unless specifically questioned.

A number of reasons may account for this decrease in dietary intake. Ablation of the stomach will abolish hunger contractions and hence decrease interest in food. A small remaining gastric pouch after subtotal gastrectomy, if it behaves as a reser-

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From the Division of Experimental Surgery and Physiology, Sloan-Kettering Institute.

Decreased stimulation of pancreatic and biliary secretions is an attractive hypothesis to account for postgastrectomy steatorrhea for several reasons: 1. On theoretical grounds, these secretions should be decreased, not only by ablation of at least part of the vagus innervation but also by suppression of the secretin response through removal of the acid-secreting glands of the stomach. 2. We demonstrated[6] a marked decrease in the secretion of canine pancreatic juice after administration of hypertonic solutions into the small bowel. 3. Colleagues and I[11] demonstrated an improvement in fat absorption in 9 of 13 patients with postgastrectomy steatorrhea when hydrochloric acid was given orally prior to meals. We presumed that this acid acts through the secretin mechanism, but the effect of change in intestinal pH also must be considered. 4. Some gastrectomized patients treated with pancreatin show reduction of steatorrhea, and Polak and Pontes[14] demonstrated a marked reduction in steatorrhea after the administration of bile salts to gastrectomized patients. 5. With use of radioiodine (I^{131})-labeled triolein and oleic acid, Shingleton and co-workers[15] demonstrated a nearly normal absorption of oleic acid in 50 patients subjected to Billroth II resection of the stomach; whereas about half of these patients showed a defect in the absorption of triolein. The addition of bile salts and pancreatic extract improved the absorption of triolein significantly. 6. Studies of fat absorption after Billroth I and Billroth II resection by several researchers[16] indicate less impairment in fat absorption after Billroth I resection. Since the Billroth I procedure channels food through the duodenum, it might be expected that there would be a more adequate mixing of the food with whatever bile and pancreatic secretions were present.

It seems logical to expect that increased intestinal motility might lead to a shortened transit time and, hence, to some degree of malabsorption. We have attempted to study intestinal transit time with different nutrients roentgenologically by combining these test meals with barium. Marked and inconsistent variations noted with this technique have made correlations of defect in fat absorption with motility extremely difficult, if not impossible. Even in patients who experience diarrhea in association with the dumping syndrome, the correlation between fat absorption and diarrhea is poor. Polak and Pontes[14] had similar experiences while feeding bile salts to gastrectomized patients. They found this form of therapy was impractical, since the doses of bile necessary to improve fat absorption invariably led to frequent watery stools.

Increased Metabolic Requirements

Schwartz and co-workers[9] have presented evidence that the protein requirement may increase after gastrectomy. Even taking into account the increase in fecal nitrogen excretion, they noted that more protein was necessary to keep gastrectomized patients in positive nitrogen balance than the control patients. An attractive hypothesis is that this wastage of nitrogen is related to the repeated stresses associated with the dumping syndrome, but, at present, there is no evidence to confirm this possibility. In any event, these authors noted a decrease in nitrogen requirement in a small group of gastrectomized patients treated with anabolic agents, such as dihydrotestosterone.

Management of Patients with Malnutrition After Gastrectomy

Paramount importance in the prevention and treatment of postoperative malnutrition is the maintenance of an adequate dietary intake. Every effort should be made to avoid or abolish symptoms which would prejudice the patient against the ingestion of food, even to the point of revising anastamoses in certain patients with the afferent loop syndrome or severe bile regurgitation. Food should be given in frequent, small feedings to avoid unpleasant symptoms of distention and to avoid debilitating symptoms of the dumping syndrome. This is particularly important in the early postoperative period when the dumping syndrome seems to occur more readily, resulting in a conditioned reflex against food.

The diet should be low in carbohydrate, not only to avoid the dumping syndrome but also to prevent excessive losses of fat in the stools. The diet should be high in protein, since it is least apt to cause the dumping syndrome and its absorption is somewhat impaired. Since the proportion of fat absorbed remains constant over a wide range of fat intake, and since neutral fats generally do not produce the dumping syndrome, needed calories should be supplied by increasing the fat intake.

The value of dietary adjuvants remains unsettled at the present time. Administration of bile salts may improve absorption of fat, but this is impractical since available preparations produce diarrhea. Pancreatic extract is rarely useful, except in patients who have had concomitant removal of the head of the pancreas. My experience with orally given hydrochloric acid is of physiological interest, but I would not recommend its use from a practical clinical standpoint except under unusual circumstances. Hydrochloric acid has the obvious disadvantages of being distasteful to some persons and capable of destroying enamel on teeth. By improving the flow of bile and pancreatic juice, it might be expected to enhance symptoms of the dumping syndrome. Finally, an increase in the incidence of recurrent or marginal ulcer would contraindicate its use after any form of partial gastrectomy.

Other adjuvants that may be of value include anabolic agents, such as dihydrotestosterone and appropriate amounts of parenteral vitamin B_{12}, if the patient develops macrocytic anemia after total gastrectomy. Finally, in the severely malnourished patient, hospitalization and transfusion are fre-

A summary of proposed changes occurring in the dumping syndrome is demonstrated in fig. 2 and is as follows: 1. Rapid hydrolysis of ingested nutrients in the jejunum leads to a hypertonic intestinal content. 2. This hypertonic material is rapidly diluted by fluid drawn from the plasma and extracellular fluid, leading to a sharp drop in circulating blood volume. 3. Drop in blood volume, decrease in cardiac output, and perhaps dilatation of the jejunum lead to decreased pancreatic secretion and a sympathetic vasomotor response producing sweating, tachycardia, electrocardiographic changes, and weakness. Changes in effective circulatory volume may be modified further by splanchnic pooling as well as autonomic "discharge."

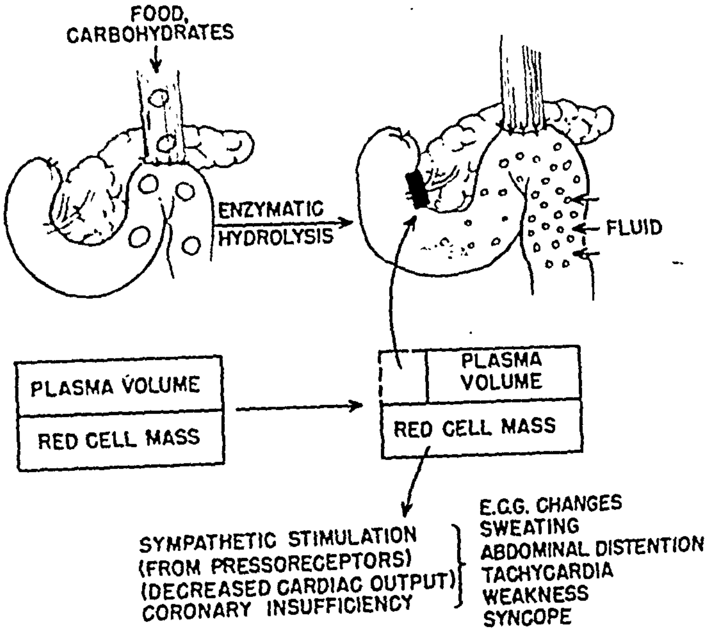


Fig. 2.—Changes occurring in dumping syndrome.

The observations concerning acute alterations in blood volume with the dumping syndrome have been confirmed by several investigators, with use of hypertonic solutions.[7] However, the incidence of significant changes in blood volume in gastrectomized patients taking regular diets, rather than test meals, remains to be determined. Previous studies of the incidence of the dumping syndrome have relied primarily on a compilation of subjective symptomatology. It is hardly surprising under these circumstances to find that Randall[1] reported an incidence of the dumping syndrome in patients after partial gastrectomy ranging from 2 to 75% and in patients subjected to total gastrectomy from 66 to 100%. Whatever the true incidence of the dumping syndrome may be, it is understandable that the aforementioned physiological responses would prejudice a number of patients against food.

Malabsorption of Food

While the major cause for malnutrition after gastrectomy is inadequate food intake, malabsorption of whatever food is ingested would contribute to malnutrition. Evidence indicates that both nitrogen and fat absorption may be defective after gastrectomy.

With 2 Gm. of nitrogen taken as the upper limit of normal fecal nitrogen excretion, Everson[8] tabulated impaired assimilation of proteins in 7 of 13 patients after total gastrectomy and in 11 of 44 patients after subtotal gastrectomy. Loss of nitrogen in the stools is rarely of great magnitude. Schwartz and associates[9] studied nitrogen metabolism in seven patients who were subjected to total gastrectomy from four months to five years previously. They demonstrated that the nitrogen losses varied from 1.8 to 3.4 Gm. per day on intakes that ranged from 8 to 24.6 Gm. They found that the percentage of fecal excretion of nitrogen decreases with higher intakes. Therefore, a modest increase in protein intake should easily provide adequate quantities for nitrogen balance.

A defect in fat absorption is also a common occurrence in patients after gastric surgery, but it is not a universal finding.[10] I have considered 92% absorption of ingested fat as the lower limit of normal. In my own studies of patients after total gastrectomy, the mean absorption was 80.8% of ingested fat, while the mean absorption in 17 patients after subtotal gastrectomy was 90.2%. Fat absorption after gastrectomy rarely goes below 70% of that ingested. However, variations within this range, which have been used by various authors to prove the merit of one type of operation over another, must be reevaluated in view of recent findings.[11] While fat absorption was not affected significantly by the amount of fat in the diet, it decreased significantly in one-half of gastrectomized patients when the carbohydrate content of the diet was doubled. Furthermore, on repeat metabolic studies, I demonstrated a definite tendency toward spontaneous improvement in fat absorption with increasing time after surgery. These two findings make it more difficult to evaluate the absolute incidence of postgastrectomy steatorrhea or the relative merit of various operative procedures.

The major possible causes for steatorrhea after gastrectomy have been enumerated by Everson[8] as follows: (1) loss of digestive function of the stomach, (2) loss of triturating function of the stomach, (3) loss of reservoir function of the stomach, (4) decreased stimulation of pancreatic and biliary secretions, (5) improper or inadequate mixing of food with pancreatic and biliary secretions, and (6) increased intestinal motility.

Everson dismissed the first two possibilities, since gastric lipase has relatively little effect on fat, and mechanical trituration of food prior to administration had no effect on steatorrhea observed in dogs after gastrectomy. Emery suggested[12] that the reservoir function of the stomach and its intermittent release of food in small amounts into the intestine may be important, since he noted improvement in fat absorption in a gastrectomized dog when small amounts of food were offered at frequent intervals. Brain and Stammers[13] found a similar improvement in fat absorption in eight gastrectomized patients given frequent small feedings.

COMMITTEE ON TOXICOLOGY

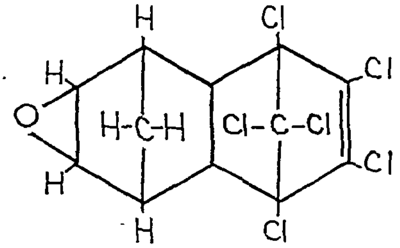
Report of the Committee

The following article, which is primarily a review of chronic occupational dieldrin poisoning in man, also includes a report of a fatal case of acute dieldrin poisoning which occurred in the home.

BERNARD E. CONLEY, Ph.D., *Secretary*

OCCUPATIONAL DIELDRIN POISONING

Dieldrin is the coined generic name for the insecticidal product containing as its principal constituent not less than 85% of the chemical 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4,5,8-dimethanonaphthalene (HEOD) and not more than 15% insecticidally active related compounds. Technical dieldrin contains not less than 90% dieldrin (76.5% HEOD). Dieldrin was developed in the United States and was made available commercially in 1948. Chemically, dieldrin is an oxygenated derivative of aldrin and resembles this compound in many aspects. It is a white, nearly odorless, crystalline solid. It is moderately soluble in aromatics, halogenated solvents, esters, and ketones; sparingly soluble in aliphatic hydrocarbons and alcohol; and insoluble in water. It is stable in the presence of organic and inorganic alkalis and dilute acids but reacts with concentrated mineral acids. The principal constituent of dieldrin has the empirical formula $C_{12}H_8OCl_6$ and the following structural formula:



Uses

High insecticidal activity combined with long residual action makes dieldrin an effective insecticide. Since 1952 it has been used extensively for the control of insects attacking principal field food and forage crops and for the control of forest pests. In many foreign countries, the use of dieldrin as a residual spray in shelters and dwellings to control vector-borne diseases has become an established epidemiological practice. It has not been approved as a residual spray for indoor application in the United States due to lack of evidence for its safe use by the person applying the insecticide and the inhabitants. Formulations accepted by the U. S. Department of Agriculture for indoor use are dieldrin oil solution, 0.5%; dust, 1%; and dieldrin emulsifiable concentrate to be diluted with water before application. Dieldrin is also marketed in 0.5% spray formulations in both liquid and pressurized forms.

Pharmacology

Dieldrin, like other chlorinated hydrocarbon insecticides, acts as a stimulant to the central nervous system. Although it has shown marked parasympathomimetic action in laboratory animals, this effect is exerted through stimulation of central mechanisms, not peripherally.[1] The mechanism of action in animals or man is not known. The principal effect on the central nervous system is increased stimulation, which culminates in one or more convulsions; these convulsions are self-remitting but recur with increasing severity. In experimental animals, large doses of dieldrin also reduce or eliminate appetite by an action on the central nervous system.

Animals poisoned by dieldrin have experienced convulsions as long as 120 days after the last dose, and in one sprayman (worker with dieldrin) the first convulsion was noted 15 days after the last exposure. The fact that symptoms have recurred in animals and man after exposure has ceased suggests the possibility that dieldrin produces morphological or biochemical lesions, or both, which persist for some time.[2]

Dieldrin is absorbed through the gastrointestinal tract, the respiratory tract, and the skin. In contrast to dichlorodiphenyltrichloroethane (DDT), the technical powder is absorbed through the intact skin almost as readily as dieldrin in solution. Furthermore, any given dosage is absorbed more readily by a large area of skin than by a small area. Thus, any increase in the area of skin exposed not only increases the dosage that will be received but also facilitates the absorption.

Information on the storage, distribution, detoxification, and excretion of this compound is scanty. In cattle, sheep, pigs, and rats, dieldrin is stored quently indicated, since patients who are cachectic and have a depleted blood volume usually cannot tolerate the acute decrease in blood volume associated with the dumping syndrome. With enforced rest, frequent feedings, and dietary reeducation, one can expect an increase in weight, blood volume, and ability to withstand the dumping syndrome.

Summary

Postoperative nutritional problems occur in about one-half of patients subjected to subtotal gastrectomy and in almost all patients subjected to total or near-total gastrectomy. The major cause of undernutrition after gastric surgery is failure of patients to eat adequate amounts of food.

Inadequate food intake is related in most instances to the dumping syndrome. Rapid hydrolysis of carbohydrate and other nutrients leads to an increased osmolar load in the small intestine, followed by a rapid influx of fluid into the intestine from the circulating blood volume and extracellular fluid space. Sympathetic vasomotor responses secondary to distention of the bowel and to the sudden drop in blood volume appear to explain most symptoms of the dumping syndrome.

Failure of absorption of fat and protein contributes to malnutrition in a substantial number of cases. The exact incidence of steatorrhea after gastrectomy is unknown, since carbohydrate intake in previous metabolic balance studies has not been controlled. A high carbohydrate intake may either precipitate or increase the defect in fat absorption. When absorptive defects do exist, they are proportionate to the amount of fat or protein ingested, so that an increased intake results in adequate absorption of the nutrient. Steatorrhea after gastrectomy may be related to inadequate secretions of bile and pancreatic juices since, in animals, production of the dumping syndrome leads to a decrease in pancreatic and probably biliary secretions. Furthermore, the administration of hydrochloric acid prior to meals, which presumably elicits a secretin response and leads to increased secretion of bile and pancreatic juices, improves fat absorption in most gastrectomized patients studied. Nutritional improvement is to be expected in most gastrectomized patients when they are fed a diet high in fat and protein but limited in carbohydrate content. Food should be given in small amounts at frequent intervals.

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characterized by one or more epileptic convulsions, with loss of consciousness but without involuntary incontinence of feces or urine.

A type of dieldrin poisoning has been observed in experimental animals which has not been described in man.[7] It is characterized by complete food refusal, rapid weight loss, and convulsions. When not treated, this form of poisoning has proved uniformly fatal. Under certain conditions it could probably occur in man.

Diagnosis of acute dieldrin poisoning is based on the history of exposure. Early symptoms of poisoning include headache, dizziness, and general malaise. Vomiting and nausea are usually present but may not occur if large doses have been absorbed rapidly. In severe poisoning, convulsions ensue and are repeated at about half-hour intervals unless treatment is instituted promptly. Coma may or may not follow the convulsions. Hyperexcitability and hyperirritability are also common findings.

Treatment

In acute poisoning, the contaminated skin should be washed with soap and water. Ingested dieldrin should be removed by gastric lavage and saline cathartic. Oils and fats are contraindicated because they promote absorption of the insecticide. Physical stimuli, which may precipitate convulsions, should be avoided. Central nervous system symptoms are controlled by barbiturates. Phenobarbital is the drug of choice because of its long action. Patients should receive as much of this drug as they will tolerate without sleeping more than the usual length of time. Further treatment consists of supportive measures.

Reported Cases of Dieldrin Poisoning in Spraymen

Country	Cases, No.	Formulation, % Concentration		Fatalities, No.
		Suspension	Emulsion	
Ecuador	8	2.50	..	1*
India†				
Bombay State	..	..	..	..
Malaria unit	10	1.25	..	0
Filaria unit	10	2.50	..	0
Indonesia	72	..	1.25	0
Nigeria	4‡	1.37	..	0
		0.68	0.68	0
Venezuela	51	1.25	2.50	0
Total	160			1

* Exposed to dieldrin: illness characterized by convulsions: circumstances of death unknown.
† Excluding Bombay state.
‡ One case history of epilepsy.

Chronic dieldrin poisoning is not likely to develop under normal conditions of good usage of the insecticide. The diagnosis is based on a history of exposure to dieldrin and the absence of any clinical history of convulsions occurring before exposure to dieldrin. There may also be a history of weight loss, headache, nervousness, difficulty in sleeping, and general malaise. Treatment consists of removing the patient from the source of exposure, supportive measures, and the administration of barbiturates to control central nervous system symptoms.

Clinical Experience

Clinical reports of poisoning in man from the use of dieldrin have not been reported in the United States. However, poisoning characterized by convulsions and associated with dieldrin and closely related compounds has been observed in industrial workers in the United States.[8] Occupational exposure to dieldrin has been associated with a number of cases of poisoning in foreign countries. Poisoning has been reported among spraymen engaged in public health programs for control of disease vectors in Ecuador, India, Indonesia, Nigeria, and Venezuela (see table). The proportion of workers poisoned in the various programs range from 2 to 40%, and the proportion of cases involving convulsions range from 47 to 100%. With the exception of one death in Ecuador, there were no fatalities after occupational exposure. The workers in these programs were not exposed to dieldrin on a continuous basis. In India, for example, spraying operations were carried out in cycles of 32, 71, and 78 days with intervals, between cycles, of 98, 63, and 31 days.

Twenty cases of poisoning were reported in Bombay State, India, 10 in the filaria unit employing 105 workers and 10 in the malaria unit employing 192 workers.[9] In the filaria unit, poisoning occurred 14 to 154 days after the first exposure to dieldrin. Severe symptoms did not develop in one patient until 15 days after the last exposure. Another patient who had not been exposed to dieldrin for eight months had a convulsion while spraying benzene hexachloride (BHC, Lindane). In the malaria unit, poisoning occurred 60 to 116 days after the first exposure. One patient showed symptoms of poisoning during the first period of exposure (60 days). In the other patients, symptoms appeared early during the second period of spraying, which followed a month of no spraying.

Symptoms showed a definite gradation ranging from giddiness, headache, and muscle twitching to convulsive attacks occurring up to several times a day, with loss of consciousness for periods up to two hours. Convulsions were characterized by violent tonic contractions, eyeballs rolling upwards, clenching of the teeth, and occasional tongue-biting. Mental disturbances ranging from loss of memory to mania were observed.

The spray teams did not wear protective clothing or masks; workmen handled and mixed the insecticide with their bare hands.

In Venezuela, 51 cases of poisoning were reported among 285 workers.[10] The earliest symptoms were observed four months after exposure.

unchanged in the body. At present, there is no information indicating the time required for a single species to reach equilibrium of dieldrin storage. It may be assumed that, during exposure, dieldrin circulates in the blood and is stored in the fat.[2] Significant amounts have been detected in the perirenal and omental fat (13 to 42 ppm), in the kidneys (4 to 32 ppm), and, in lesser amounts (1 to 7 ppm), in the brain, liver, and testes of rats.

Although the mechanism for detoxification and excretion has not yet been determined, it has been clearly established that dieldrin is dissipated from body tissues after cessation of exposure.

Histopathological changes in animals poisoned by dieldrin are similar to those produced by other chlorinated insecticides and are nonspecific. Varying degrees of degeneration of the kidney tubules may be produced, and swelling and protoplasmic changes in the liver cells may be observed. There are no definite changes in the central nervous system. Pulmonary edema and endocarditis, which may follow convulsions from any cause, may also be produced.

Toxicity

The fatal oral dose of dieldrin in humans is not known. Untoward symptoms have occurred in man after oral doses as small as 10 mg. per kilogram of body weight. In rats, the acute oral LD_{50} of dieldrin ranges from 37 to 87 mg. per kilogram of body weight. This difference in values is apparently due to the grade of dieldrin tested and the nature of the solvent. The approximate mean lethal oral dose for rats is 65 mg. per kilogram of body weight. This is believed to be a reasonable estimate of the lethal dose in man. Dieldrin is less than twice as toxic by ingestion as by skin absorption. Its oral toxicity is three to five times greater than that of DDT. One incomplete case history of a fatality has been reported of a man who ingested an unknown quantity of dieldrin.

Nothing is known quantitatively about chronic oral toxicity in man. The fact that dieldrin produces toxic symptoms when fed to animals in sublethal doses over an extended period of time has been established.

The acute dermal toxicity of dieldrin in xylene is approximately 40 times that of DDT. There is considerable difference in the LD_{50} values for different species[3]; the acute dermal LD_{50} value for white rats is 90 mg. per kilogram of body weight for males and 60 mg. per kilogram of body weight for females; for rabbits the range is 400 to 450 mg. per kilogram of body weight. Such inconsistent ranges of dermal toxicity make it difficult to estimate a value for man. There is no information on chronic dermal toxicity of dieldrin to man and little information on that to animals.

Although it has been commonly assumed that respiratory exposure in man is the major source of occupational poisoning, under certain circumstances dermal exposure is the greatest occupational hazard. Chemical measurements of "imperceptible contamination" (constant contamination of the bare skin, and, to a lesser degree, the protected skin) have shown the relative unimportance of respiratory exposure.[4] Dieldrin is toxic when inhaled. However, poisoning due to respiratory exposure is not likely to occur during spraying operations, for almost all dieldrin in water-dispersible powders is in particles too large to be inhaled.

Laboratory Findings

A satisfactory method for measuring the absorption of dieldrin has not yet been developed. Laboratory findings are essentially negative and of little diagnostic value. At present, there are no laboratory tests which specifically indicate increased absorption or true intoxication. Although there is a method for measuring dieldrin in fat, no methods are available for measuring dieldrin or its derivatives in the blood or excreta.

The presence of some chlorinated hydrocarbon insecticides has been detected experimentally by bioassay. This method has been used in spraymen poisoned by dieldrin[5]; however, it indicated only a broad parallelism between symptomatology and the concentration of dieldrin in the blood and showed such individual variation that it has limited diagnostic value.

Electroencephalography has also been used to study dieldrin poisoning.[6] Electroencephalograms were abnormal in about half of the clinical patients, showed a small degree of abnormality in some patients, and no detectable abnormality in others. However, the electroencephalograms also showed abnormal findings in a few unexposed persons. Similarly, considerable work with other methods of testing, such as urinalysis, complete blood study, chest x-ray, determination of visual fields, and psychological tests, has failed to show their value as diagnostic aids in determining dieldrin poisoning.

Diagnosis

Dieldrin intoxication observed in man has been described in terms of three degrees of clinical illness[5b]: 1. Mild intoxication is characterized by headache, blurred vision, dizziness, slight involuntary muscular movements, sweating, difficuty in sleeping and bad dreams, nausea, and general malaise. 2. More severe illness involves the aforementioned symptoms plus stronger jerking motions of entire muscle groups, some motions even causing the victim to fall. In extreme cases, these movements are accompanied by momentary loss of consciousness. 3. The most severe nonfatal illness is

PRELIMINARY COMMUNICATION

BRETYLIUM TOSYLATE AS AN ANTIHYPERTENSIVE DRUG

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In severely hypertensive patients ganglioplegic drugs exert a more predictable depressor effect than other antihypertensive agents. They are used infrequently in mildly hypertensive patients, because side-effects from parasympathetic blockade are too troublesome. A drug decreasing sympathetic overactivity without affecting parasympathetic function would be expected to have the hypotensive action of ganglioplegics without their unpleasant side-effects. Bretylium has this property. Studies by Boura and associates[1] have shown that bretylium selectively blocks the function of the peripheral sympathetic adrenergic nerves. This effect appears after systemic injection and when the nerves are bathed in bretylium-containing solutions. Results of pharmacological tests suggest that the mechanism of action is due to impairment of norepinephrine production by nerve endings. Parasympathetic function was not inhibited. Intravenously injected bretylium produced slight decreases in supine arterial pressure in normotensive and hypertensive human subjects; orthostatic hypotension was pronounced. Early clinical studies[1a] showed orally given bretylium tosylate to be an effective antihypertensive agent. Our report describes further experience with bretylium.

Method

Thirteen hypertensive patients were hospitalized for study and institution of treatment. Seven patients had been receiving other antihypertensive drugs, which were discontinued because of either poor blood pressure control or troublesome side-effects; six had had no prior therapy. Brachial arterial pressure was measured four times daily in both the supine and standing positions during hospitalization and at home after hospital discharge. The severity of hypertensive cardiovascular disease was estimated during the control period by use of a numerical severity index described elsewhere.[2] Urine protein excretion, total white blood cell and differential counts, and blood hemoglobin content were measured weekly. Frequent tests of sulfobromophthalein excretion were performed.

After suitable control periods without medication, bretylium tosylate was given four times daily before meals and at bedtime in gradually increasing amounts until final doses of 2 to 8 Gm. per day had been reached. A weekly average supine diastolic blood pressure less than 105 mm. Hg was considered an adequate hypotensive response. Eight patients, who failed to achieve or sustain such responses, received additional antihypertensive drugs. Arterial pressure responsiveness to intravenous administration (0.5 mg. per kilogram of body weight) was studied in three patients before and during oral treatment, and in three such observations were made only during treatment.

Results

Hypotensive Effects.—Orthostatic hypotension, which was well tolerated, developed in all patients receiving bretylium tosylate (table 1). In six, supine diastolic pressure fell to less than 105 mm. Hg, but in four this was not sustained and pressure gradually rose to previous levels, although orthostatic hypotension persisted. In the other seven, diastolic pressure decreased but not to levels less than 105 mm. Hg.

When the decrease in supine diastolic pressure was not maintained or the initial hypotensive response was not adequate, other drugs were added. Thus, eight patients received additional therapy, with either hydrochlorothiazide, hydralazine, or phentolamine. A satisfactory fall in supine diastolic pressure occurred in six; in two no further reduction was obtained. In the six who had a decrease in supine diastolic pressure with bretylium and with another drug, arterial pressure gradually rose after two to three weeks and approached control values or those obtained with bretylium alone. Thus, bretylium failed to achieve sustained decreases in supine diastolic pressure over several weeks of therapy. In only two patients has a good response been maintained for as long as two to five months. Further, orthostatic hypotension, although persisting, tended to lessen as time went on. To investigate the possibility of poor drug absorption as a cause of these results, the dosage was increased in five patients and no further decrease of either supine or standing arterial pressure occurred.

Response to Intravenously Given Bretylium Tosylate.—Prior to the initiation of oral treatment three patients were given 0.5 mg. per kilogram of body weight of bretylium tosylate intravenously (table 2). In two to four hours a slight decrease in supine blood pressure occurred. Repeated intravenous test doses were given to these three patients and an additional three during the course of chronic oral

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The greatest incidence of poisoning occurred in workers who had been exposed from 12 to 19 months.

The same gradation of symptoms that characterized the Indian patients were observed in these patients. Convulsions occurred in 24 patients. Details of laboratory findings were not characteristic; the electroencephalograms often showed abnormal findings, with signs of cortical irritation. Response to treatment was usually prompt, but recovery was delayed in some cases, the longest time being 105 days. Treatment consisted of removal from exposure and supportive measures. Recovery was complete, with no sequelae.

Experience with these cases of occupational dieldrin poisoning provide evidence that dieldrin poisoning in man tends to be chronic. However, the following case history is a report of a fatal case of acute dieldrin poisoning. This accidental poisoning, which occurred in an infant in her home, is probably the first full report of death from dieldrin poisoning in man.

Report of a Case

On April 10, 1958, a nine-month-old girl from one of the villages in the neighborhood of Ramlah was admitted to the children's department of the "Assaf Harofe" Government Hospital. Her condition was critical. Her mother related that about six hours before she had found her daughter sitting on the floor near some loose insecticide powder which was on a piece of paper. The face of the child apparently had been buried in the powder. Her mother immediately washed her face with water and rinsed the infant's mouth with water. After six hours she suddenly lost consciousness and became dyspneic and cyanotic, and a few seconds later convulsions began. She was admitted to our ward in this condition. Dyspnea, cyanosis around the mouth, horizontal nystagmus, patellar reflexes, and unconscious, clonic convulsions in her upper and lower limbs and in the muscles of the face were observed. No pathological reflexes were recorded. Examination of other organs showed no deviation from normal. She remained in this condition for about 14 hours, despite therapy with recurrent large quantities of phenobarbital, chloral hydrate, and chlorpromazine. Finally the convulsions stopped, but she still remained unconscious; her temperature rose to 104 F (40 C), the dyspnea and cyanosis grew worse, and severe tachycardia occurred. The child died about 20 hours after ingestion of the poison. The post-mortem examination revealed hypostasis of both lungs, small foci of necrosis of the liver, and edema of the epithelia of the renal tubules (fig. 1 and 2).

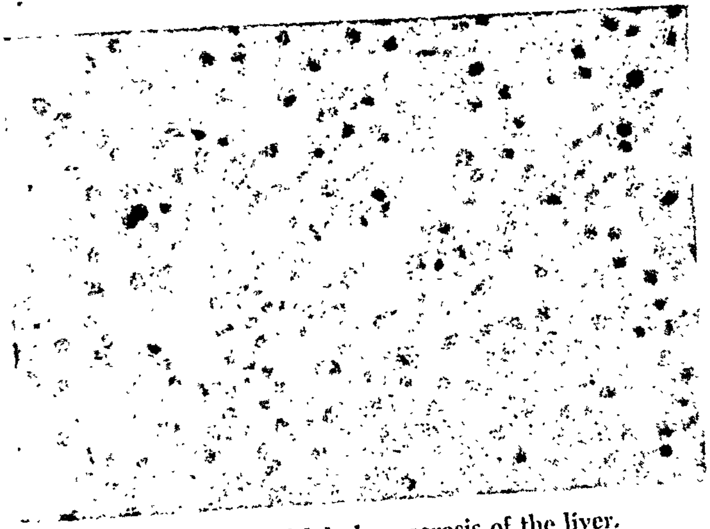
Fig. 1.—Central lobular necrosis of the liver.

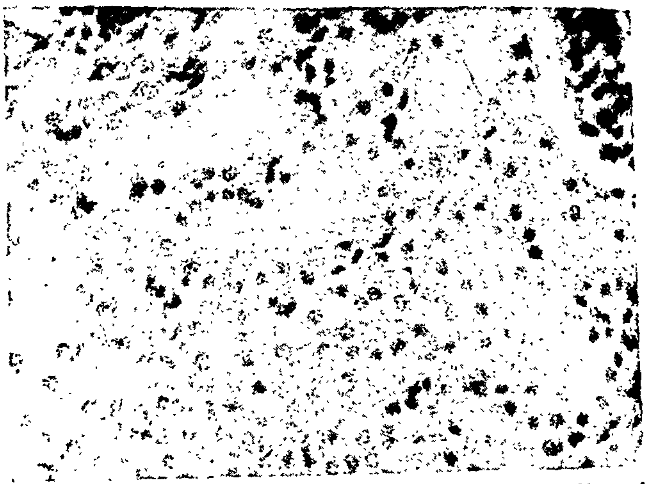
Fig. 2.—Moderate degeneration of tubular epithelium of the kidney.

The insecticide she had ingested contained 4% dieldrin; however, the dosage ingested was not known. A few days earlier her father had applied this compound to watermelon plants. The remainder had not been properly disposed of, so that the child became the victim of her parents' negligence.

The case report was contributed by Anatola Kalushiner, M.D., from the Children's Department A', "Assaf Harofe" Government Hospital, Sarafand, Israel.

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and maintenance of orthostatic hypotension as the criterion of a good response, our results show bretylium to be an effective antihypertensive agent. This experience is in accord with those of Boura and others [1a] and of Smirk and Hodge,[4] both of whom emphasized the orthostatic hypotensive effects of the drug. If the criterion is maintenance of supine diastolic pressure at 105 mm. Hg or less, however, this was fulfilled by only 2 of the 13 patients treated with bretylium.

Either the development of tolerance to the hypotensive effects of the drug, or a progressive decrease in absorption from the gastrointestinal tract, was suggested by only transient reduction in arterial pressure by bretylium or by bretylium plus other antihypertensive drugs. These possibilities were examined by evaluating hypotensive responses to bretylium given intravenously during oral treatment.

In four patients given an intravenous test dose during the early weeks and in two others after 10 to 14 weeks of oral administration of bretylium a depressor response occurred despite large daily oral doses; this indicates poor drug absorption, as suggested by Boura and co-workers.[1a] However, in two patients no depressor response was seen after 15 to 20 weeks of oral treatment. In patient 11 some orthostatic hypotension persisted two weeks after discontinuation of the drug; at this time an intravenous test dose failed to lower supine arterial pressure. These results suggest development of tolerance and are in accord with the pharmacological studies of Boura and Green.[1b]

Facial pain has been a troublesome feature of bretylium treatment because it has persisted and, in some patients, become more severe with continued therapy. It is unlike the parotid complaints, seen occasionally in patients treated with ganglioplegic drugs, which seemed due to plugging of Stenson's ducts by inspissated salivary secretions. Rather, the difficulty encountered with bretylium suggests that it results from some functional change within the walls of the ducts; this is indicated by the transient nature of the discomfort and by the finding that, in one patient, the volume and character of salivary secretion was normal. The cause of the abdominal pain is obscure; elevation of serum amylase concentrations may reflect some abnormality of pancreatic duct function.

Table 2.—*Effects of Intravenous Test Doses of Bretylium Tosylate Before and During Chronic Oral Therapy*

Patient, No.	Average Weekly Blood Pressure, Mm.Hg.* L	S	Wk. of Therapy	I.V. Test—Supine Blood Pressure, Mm.Hg. Control	Lowest	Change	Daily† Oral Dose, Gm.
6..........	188/107	138/ 88	2	182/ 90	127/ 67	—55/—23	6.8
	183/115	157/109	15	182/110	154/ 98	—28/—12	4.0
	183/115	157/109	15	220/120	210/118	—10/— 2	8.0
8..........	198/116	171/111	Control	189/109	167/ 98	—22/—11	0.0
	168/109	129/ 97	14	174/112	156/100	—18/—12	4.4
	174/114	124/ 85	20	156/100	150/100	— 6/0	6.4
	174/114	124/ 85	20	146/ 98	142/ 98	— 4/0	8.0
9..........	136/ 99	71/ 57	3	162/114	130/104	—32/—10	3.2
	164/118	110/ 95	15	150/110	150/110	0/0	2.0
11..........	163/118	123/ 99	10	174/122	128/ 90	—46/—32	4.8
	175/132	139/118	17	188/120	192/120	+4/0	0.0‡
12..........	189/126	182/138	Control	192/117	180/110	—12/— 7	0.0
	178/117	105/ 73	2	154/107	130/100	—24/— 7	7.2
13..........	189/132	174/133	Control	199/122	180/115	—19/— 7	0.0
	178/131	95/ 74	3	215/141	170/120	—45/—21	4.8

* L: supine blood pressure; S: standing blood pressure.
† For at least 3 days prior to test dose.
‡ Bretylium therapy stopped 2 weeks before intravenous test.

Table 3.—*Side-Effects of Bretylium Tosylate*

Patient, No.	Facial Pain	Abdominal Pain	Appeared During Wk., No.	Dosage, Gm./Day
1..........................	++++	++++	8	2.0
2..........................	++	...	19	4.2
3..........................	+++	++	2	3.0
4..........................	++	...	17	1.0
5..........................	++++	++++	14	2.4
6..........................	++	...	13	5.2
7..........................	...	...	...	2.0
8..........................	++	...	6	1.0
9..........................	++	...	9	2.0
10..........................	...	...	...	1.8
11..........................	++	...	5	1.4
12..........................	+	...	1	7.2
13..........................	...	++++	7	7.2

Summary

Thirteen hypertensive patients were treated with bretylium tosylate for from 5 to 24 weeks. Orthostatic hypotension developed in all. Six patients receiving bretylium alone had a fall in supine diastolic blood pressure to less than 105 mm. Hg; this was sustained in only two patients and the other four showed a gradual rise to previous values. Six of eight patients receiving bretylium and other antihypertensive drugs had a transient fall in supine diastolic pressures to less than 105 mm. Hg. Studies made with repeated intravenous test doses of bretylium suggest that the drug is poorly absorbed and that drug tolerance develops with prolonged therapy. Troublesome facial pain was a prominent feature and, in conjunction with severe abdominal symptoms, required stopping administration of the drug in three patients. With use of our criterion for good blood pressure control, which is maintenance of supine diastolic pressure averages of less than 105 mm. Hg, bretylium tosylate was an ineffective antihypertensive agent in 11 of the 13 patients treated.

The bretylium tosylate used in this study was supplied as Darenthin by Dr. S. T. Bloomfield, Burroughs Wellcome & Co., Inc., Tuckahoe, N. Y.

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administration. A fall in supine blood pressure occurred after intravenous administration of bretylium during the first three weeks of oral therapy in four patients (6, 9, 12, and 13). Depressor responses were also seen 10 to 14 weeks after institution of treatment in three patients (6, 8, and 11). In two patients (8 and 9) no response was seen when the test was given after 15 to 20 weeks of oral administration of bretylium. In patient 11 a test dose of bretylium during the 10th week of treatment caused a fall in arterial pressure to normal levels. At 15 weeks she discontinued therapy, and 2 weeks later intravenously given bretylium had no effect.

Side-Effects.—Four male patients experienced increased libido and an increased potency, with no ejaculation although the sensation of climax was present; in two ejaculation has returned. No menstrual irregularities or increased sexual desires have been noted in the female patients.

Ten patients developed bilateral facial pain in the parotid area (table 3). Typically, this was described as severe, sharp pain, occurring with the first few bites of food, which lessened as mastication continued. In all there was tenderness to palpation in the parotid area, especially over the tail of the gland, with no glandular enlargement. Examination of Stenson's duct revealed no abnormalities and in one patient cannulation of the ducts yielded normal fluid volumes in response to citric acid administration; mouth dryness did not occur. Discomfort ameliorated slowly after therapy with the drug was discontinued. In two patients (1 and 5) facial pain became severe, almost continuous, and was associated with severe abdominal pain, nausea, and vomiting. There were no abnormal abdominal findings; results of liver function tests were normal; no changes in stool characteristics were noted; and an elevated serum amylase level was present. When administration of bretylium was stopped the abdominal symptoms disappeared promptly, and the serum amylase level returned to normal limits two to three weeks later. Patient 3 developed moderate facial pain with intermittent attacks of abdominal pain; while the facial discomfort has persisted, the abdominal pain has become less frequent and severe with continued treatment. Patient 13 developed severe epigastric burning pain, with nausea and vomiting, which disappeared when treatment was discontinued. The cause of this episode is obscure, since this patient was subsequently found to have a moderate-sized hiatal hernia.

Urine protein excretion, blood urea and serum creatinine levels, and urea clearance remained the same or improved. Blood hemoglobin levels, total white blood cell and differential counts, and sulfobromophthalein excretion were not affected.

Table 1.—*Antihypertensive Effects of Bretylium Tosylate Alone or with Other Antihypertensive Drugs*

			Blood Pressure, Mm.Hg‡					"Combination" Therapy									
			Control		Lowest with Bretylium Tosylate Alone					Lowest Blood Pressure, Mm.Hg			Blood Pressure Last Wk., Mm.Hg			Maintenance Dose (Gm./Day)	
Patient, No.	Dx*	TSI†	L	S	L	S	Wk., No.	Drug§	Wk. Added	L	S	Wk., No.	L	S	Wk., No.	First	Last
1	MHR	9.0	260/138	230/140	191/111	121/90	4						218/130	141/102	13	2.0	2.0
2	RAD	4.0	218/116	209/123	163/ 99	108/72	3						161/109	119/ 81	23	2.6	4.2
3	EH	5.5	212/124	206/129	190/109	160/96	3	HC	5	172/90	102/76	13	190/107	120/ 83	18	3.0	3.0
4	MH	8.5	198/122	191/121	161/ 91	106/73	8						173/ 98	115/ 77	21	4.0	4.0
5	LE	6.5	197/109	172/103	221/ 87	184/91	13						214/120	144/ 99	16	1.2	2.4
6	EH	6.5	193/114	154/112	181/101	126/82	3	HC	5	155/92	116/80	6	200/124	163/113	21	4.0	8.0
7	EH	6.5	228/136	208/138	188/115	91/67	2	HC	6	180/122	94/82	7	187/128	95/ 85	21	2.0	2.0
8	EH	5.5	198/116	171/111	178/108	128/88	2	HC	5	150/94	108/80	7	174/114	124/ 85	20	4.0	6.4
9	PK	4.5	162/107	153/114	155/101	76/61	2	Ph	3	136/99	71/57	3	164/118	110/ 95	15	2.0	2.0
10	EH	3.0	171/110	168/122	137/ 87	104/72	3						156/ 94	137/ 93	8	4.8	4.8
11	MHR	5.5	207/127	180/132	185/112	120/94	2	HC	3	143/95	98/78	5	163/116	113/ 89	15	4.4	6.4
12	EH	4.5	189/126	182/138	178/117	105/73	2	Hyd	3	144/99	84/64	3	158/109	123/ 95	10	7.2	7.2
13	EH	6.0	189/132	174/133	185/126	111/87	1	Hyd	5	169/125	89/78	5	169/125	89/ 78	5	7.2	7.2

* Dx: Diagnosis. MHR, malignant hypertension reversed by treatment; RAD, occlusive renal artery disease; EH, essential hypertension; MH, malignant hypertension; LE, disseminated lupus erythematosus; PK, polycystic kidney disease.

† TSI: total severity index.

‡ L: supine blood pressure; S: standing blood pressure.

§ HC: hydrochlorothiazide; Ph: phentolamine; Hyd: hydralazine.

Comment

At present, clinical evaluation of a new antihypertensive drug requires establishment of arbitrary criteria of effectiveness. This is because none of the available agents elicits normal arterial pressure levels in all hypertensive patients. The choice of a level to which arterial pressure must be reduced to classify a drug as effectively antihypertensive depends in part on the investigator's opinion of the relationship between the height of the blood pressure and its complications. It has previously been shown[3] that long-term survival of treated patients with malignant hypertension was partly related to the adequacy of control of supine diastolic blood pressure. As antihypertensive drugs have become better and our ability to use them effectively has increased, we do not believe a supine diastolic arterial pressure average of 110 mm. Hg represents adequate control. We now accept levels of 105 mm. Hg or less as good control. Orthostatic hypotension alone is not considered an adequate criterion for a good response.

Since most antihypertensive drugs cause orthostatic hypotension, attention has been focused on this characteristic. If one accepts the development intestinal obstruction in the newborn infant (so-called meconium ileus) rectal prolapse, abdominal masses of fecal origin, hepatic cirrhosis, and, less commonly, pancreatitis, pancreatic lithiasis, and diabetes mellitus are also seen. Massive salt loss through sweat in hot weather may lead to serious and even fatal complications. Bleeding due to hypoprothrombinemia consequent to vitamin K deficiency and severe gastrointestinal hemorrhage because of portal hypertension also occur. In all of these patients and regardless of their pancreatic functions sweat electrolyte levels are elevated. Because of its simplicity and reliability the "sweat test" is, therefore, the cornerstone of diagnosis of cystic fibrosis.

Pulmonary involvement dominates the clinical picture and determines the fate of the patients; therapy of the chronic lung disease with antibiotic agents deserves the major emphasis. The effects of pancreatic deficiency, when it is present, are less important to the ultimate outlook of the patient and generally not difficult to offset by dietary measures. The prognosis, although guarded, has been increasingly favorable as far as life span is concerned. Many patients now survive to adolescence or young adulthood. Some persons in whom pulmonary involvement is slight are doing very well in their late teens or early 20's. Early diagnosis and treatment are essential before the pulmonary disease has caused irreversible changes in the bronchi.

In addition to attempting to improve diagnostic and therapeutic methods, recent investigations in cystic fibrosis have been directed to further clarification of the genetic mechanisms, chemical structure of mucous in various body secretions, and electrolyte patterns in this disease, in an attempt to elucidate and uncover the basic mechanism responsible for the disease. One of the most challenging of the recent developments is the possible relation of this syndrome to some chronic pulmonary and gastrointestinal disorders of adults. According to Koch,[3] cystic fibrosis may prove to be even commoner in adults than in children.

Additional studies are needed to clarify the problems outlined and to interpret the facts brought to light by recent investigations. It is evident that cystic fibrosis in the homozygous and heterozygous state presents a problem of increasing importance not only to the pediatrician but to the general practitioner, the internist, and the specialists in chest diseases or gastroenterology. Cystic fibrosis is breaking out of the pediatric bounds to which it had earlier been limited by its high mortality in infancy and childhood and is now invading the domain of diseases of the adult. In its broader aspects it is not only a medical health problem but a social one as well, because of the devastating effects of the emotional and financial stress on the family of the patients. Increasing awareness by the public and the medical profession of the challenge presented by this disease has led to the establishment by the U. S. Public Health Service at the National Institute for Metabolic Diseases and Arthritis of a center for the further study of cystic fibrosis.

THE AIR WE BREATHE

By rights the air we breathe is a mixture of oxygen, nitrogen, and argon, with traces of helium, neon, krypton, and xenon, and presumably it has been approximately so since man began to breathe. Today, however, in numerous places on the earth, the air contains hundreds of substances which were never intended to be inhaled. Some of these make us uncomfortable or ill and at times hasten the end of human beings.

Extraneous substances such as dusts have been in the air for a very long time, and, while they protect us against the sun's actinic rays, they too have taken their toll. The more serious air pollution problem began well after the industrial revolution (1870), and it has increased year by year until the number of air pollutants is now almost as great as the number of human activities which produce them.

The chief air pollutants today are the oxides of nitrogen, the oxides of sulphur, the aldehydes, carbon monoxide, smoke, condensed fumes, and organic vapors, often referred to as hydrocarbons, of which there are said to be 200 in automobile exhaust fumes alone.

Automobile engines, according to Chambers, emit an average of 200 to 400 lb. (91 to 182 kg.) of hydrocarbons and from 25 to 75 lb. (11 to 34 kg.) of oxides of nitrogen, estimated as NO_2, per 1,000 gal. of gasoline used. Burning a ton of coal produces 8 lb. (3.6 kg.) of oxides of nitrogen, estimated as NO_2. Carbon monoxide is produced by gasoline engines in normal operation at the rate of about 3,200 lb. (1,453 kg.) per 1,000 gal. of gasoline. Diesel engines produce about 75 lb. of oxides of nitrogen, estimated as NO_2, per 1,000 gal. of oil burned.

One need only look at the window sills occasionally to see that the air we breathe in congested areas contains thousands of specks of soot. As for dust, for example, the Armour Research Foundation of the Illinois Institute of Technology reported that the average fall for 30 days of January, 1960, for the city of Chicago was 53.1 tons per square

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1. Proceedings of National Conference on Air Pollution, Washington, D. C., Nov. 18-20, 1958, U. S. Department of Health, Education, and Welfare, Public Health Service, 1959.
2. Mills, C. A.: Respiratory and Cardiac Deaths in Los Angeles Smogs, Am. J. M. Sc. **233**:379-386 (April) 1957.
3. Dyktor, H. G.: Community Problem, Indust. Med. **19**:102-106 (March) 1950.

THE JOURNAL
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CYSTIC FIBROSIS OF THE PANCREAS

UNKNOWN until 25 years ago, cystic fibrosis of the pancreas is now thought to be one of the most common and one of the most serious chronic diseases of childhood. In a recent survey by the United States Public Health Service Children's Bureau[1] it was concluded that cystic fibrosis poses a serious public health menace and far outweighs, as a cause of mortality in children, such well-known diseases as rheumatic fever, diabetes, or poliomyelitis. Two communications by Di Sant'Agnese in this issue of THE JOURNAL are devoted to this subject. Named by Fanconi, in 1936, it was recognized as a separate disease entity only in 1938, after the investigations of Andersen, Blackfan and May, and Harper. Cystic fibrosis of the pancreas (also known as fibrocystic disease of the pancreas and mucoviscidosis) is a generalized hereditary disease of children, adolescents, and young adults, in which a dysfunction of exocrine glands leads to chronic pulmonary disease, pancreatic insufficiency, abnormally high sweat electrolyte levels, and, at times, cirrhosis of the liver. Incomplete forms of this disorder, in which some but not all manifestations of the syndrome are present and which lead to many variations in the clinical picture, are being recognized with increasing frequency. Despite its name, cystic fibrosis is thus not a disease of the pancreas but one in which this organ is frequently, although not necessarily, involved.

Pathological changes may be found in mucous glands throughout the body, with accumulation of abnormal secretions leading to dilatation of glandular structures. The main pathological lesions are present in the pancreas and in the liver. No histological changes are seen in non-mucous producing exocrine glands (e. g., sweat and parotid glands), even though the chemical composition of their secretory products is very abnormal. The basic defect, as yet unknown, appears to be genetically transmitted as a recessive trait, and, therefore, both parents must presumably carry the recessive gene. The expected over-all incidence of cystic fibrosis among children of affected families is one in four siblings. However, in some family groups it is much higher, thus frequently putting an almost unbearable emotional and financial strain on the parents. The frequency of the gene in the general population has been estimated as high as 5 to 20%.

Evidence is accumulating that homozygotic persons show the full disease picture and that heterozygotic persons exhibit either no detectable change or only some manifestation of the disorder. In 20 to 30% of relatives (children and adults) of known patients elevated sweat electrolyte levels are the only abnormal finding. The incidence of cystic fibrosis in its fully manifested form has been variously estimated as 1 or 1.5 per 1,000 live births. It affects equally all Caucasoid groups, is rare in negroid persons, and has never been reported in Mongoloid patients.

Prior to 1938 most patients with cystic fibrosis died of bronchopneumonia in infancy or early childhood, while some, in whom the symptoms of intestinal malabsorption predominated, were diagnosed as having celiac disease. The basic disorder, cystic fibrosis, was unrecognized. The increase in the number of patients observed in recent years is due to two developments: the advent of effective antibiotic agents which markedly increased the patient's life span and the greatly improved diagnostic measures which followed the discovery by Di Sant'Agnese and associates[2] of a unique abnormality in the electrolyte comparison of sweat in 99% of patients with this disease.

The generalized disease, cystic fibrosis, gives rise to manifold clinical manifestations, apparently unrelated to each other. It is beyond the scope of this editorial to elaborate on these symptoms, but a listing may give an idea of the complexity of the diagnostic and therapeutic problems faced by physicians. Cystic fibrosis gives rise to symptoms primarily by involvement of three areas, the respiratory tract, the abdominal organs, and the sweat glands. Chronic lung disease and all of its attendant complications (atelectasis, lung abscesses, spontaneous pneumothorax, hemoptysis, cor pulmonale, and many others) are usually present. Pancreatic achylia is found in 80% of patients.

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1. Sirken, M. G.; Crane, M. M.; Brown, M. L.; and Kramm, E. R.: National Hospital Survey of Cystic Fibrosis, Pub. Health Rep. 74:764-770 (Sept.) 1959.
2. Di Sant'Agnese, P. A.; Darling, R. C.; Perera, G. A., and Shea, E.: Abnormal Electrolyte Composition of Sweat in Cystic Fibrosis of Pancreas, Pediatrics 12:549-563 (Nov.) 1953.
3. Koch, E.: Die erbliche Erwachsenen-Mucoviscidosis und ihre Beziehungen zur Ulkuskrankheit, Deutsche med. Wchnschr. 84:1773-1784 (Sept. 25) 1959.

managers of buildings, home owners, industries, and research workers, will do their part in keeping toxic material out of the air we breathe.

THE ANATOMICAL AMPHITHEATER IN PADUA AND UPPSALA

Among the most impressive material evidences of past major medical events are the temples of Asclepius in Greece and the Fabrician Amphitheater in Padua. In each instance, partial or complete restoration has helped preserve the vividness of the original. It was in the Anatomical Amphitheater in the municipal museum of the old University in Padua, Italy, that modern medicine was born. Fabricius of Aquapendente, successor to Vesalius and pupil of Falloppio, in this notable building taught Harvey the basic precepts that led him to discover the circulation of the blood.

The pulmonary circulation had been discovered earlier by a Spaniard, Michael Servetus (1511-1553), whose path had crossed that of Vesalius in Paris. Like Vesalius, Servetus doubted Galen's doctrine that the existence of blood in both chambers of the heart was due to imperceptible perforations in the septum of the heart. Servetus reasoned that the blood must enter the lungs by way of the pulmonary artery in greater quantities than is necessary for the nutrition of the lungs and that after being mixed with the *pneuma* of the lung it must return to the heart by the pulmonary vein. Servetus further stated, "If anyone compares these things with those which Galen wrote . . . he will thoroughly understand a truth which was unknown to Galen." Servetus published these daring thoughts in a theological work on the restoration of Christianity (*Christianismi Restituto*). Both his unorthodox religious views and his statements that cast doubt upon the teachings of Galen were considered heresy by Protestants and Catholics alike. Hunted by the Catholic Inquisition he fled, but in passing through Geneva he was arrested by Calvin and together with his books was condemned to perish at the stake in 1553. Only three copies of his daring treatise survived. Servetus may have been influenced in his anatomic reasoning by the writings of Vesalius, whom he had succeeded in Paris as an assistant to the anatomist Gunther of Andernach.

The 400th anniversary, in 1943, of the printing of Vesalius' magnificent *De humani corporis fabrica* was marked by the publication of the bio-bibliography of Andreas Vesalius by Harvey Cushing.[1] The bio-bibliography contains a large amount of reference material on Vesalius and especially on *De fabrica*. Sir William Osler as well as Harvey Cushing was a devout worshiper of Vesalius. Cushing recounts that on one occasion Osler had boasted of six copies of *Fabrica* collected on one of his barnstorming tours in Europe. "As a book, *Fabrica* has probably been more admired and less read than any publication of equal significance in the history of science. That it was an amazing tour de force for a young man in his late twenties, however industrious and inspired he may have been, goes without saying."

The frontispiece of *Fabrica* was designed by Jan Calkar, a pupil of Titian. The woodcuts were prepared in Padua and processed in Basel. The frontispiece is second in significance only to Harvey's line drawings illustrating the circulation of blood. Vesalius states in the dedicatory preface, "I have done my best to this single end, namely, in an equally recondite and laborious manner, to aid as many as possible, and truly and completely to describe the structure of the human body—which is built up, not of some ten or twelve parts (as seems to those who give it a passing glance), but of some thousands of different parts—and to bring to students of medicine a substantial contribution toward the understanding of those books of Galen treating of this branch of learning, which of all writings most require the assistance of a teacher. Moreover, I am aware how little authority my efforts will carry by reason of my youth (28 years) and how little, on account of the frequency with which I draw attention to the falsity of Galen's pronouncements. I shall be sheltered from the attacks of those who have not—as I have done in the schools of Italy—applied themselves earnestly to anatomy, and who being now old men devoured by envy at the true discovery of youth's will be ashamed, together with all other sectaries of Galen, that they have been hitherto so purblind, failing to notice what I now set forth, yet arrogantly to themselves a mighty reputation."

The Anatomical Amphitheater which was inspired by Vesalius and built by his successor can still be visited in the old University of Padua. Built in the shape of a steep funnel, it has a six-tiered pit in which there are no seats; the narrow space leaves room for standing only. If one, by chance, is traveling north from Padua and into Sweden, it is worth noting that a second anatomic amphitheater has been restored in Uppsala. This structure was designed as a precise replica of the amphitheater in Padua, only a few years later. It has been maintained with the same vigilance as the original.

JOURNAL INDEX

The index to volume 172 of The Journal will appear in the May 14 issue. Those who wish extra copies of the index may receive them, without charge, on request to the Circulation and Records Department, American Medical Association, 535 N. Dearborn St., Chicago 10.

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[1] Cushing, H.: Bio-Bibliography of Andreas Vesalius, New York, Schuman's, 1943.

mile, while in the Chicago Loop it was 124.1 tons per square mile. The list could be extended for both places and things.

In this issue of THE JOURNAL, Oderr reports (page 1991) a study of 200 lungs of adults who died of causes other than tuberculosis or lung cancer. He observed a correlation between parenchymal soot deposit and emphysema. His findings indicate that the common form of chronic emphysema begins in highly localized areas which tended to be in the pathways trapping soot particles. Lawther, at St. Bartholomew's Hospital in London, found that certain soot particles trap acid radicles internally, and when they are collected on cascade impactor slides coated with gelatin films containing a color indicator, a strongly acid reaction is observed after a time. Other mechanisms have been suggested by which air-polluting inhalants could produce structural and functional abnormalities in the lung.

The effects on public health of unsavory gases and solids in the air is of first importance. It seems obvious, in some places, that the effects have been detrimental. However, as yet scientific proof of the specific hazards to human health is fragmentary, making it difficult to arrive at valid conclusions. Many studies have been published; many are under way. The Proceedings of the National Conference on Air Pollution, sponsored by the U. S. Public Health Service, published recently, contains much of the information here being reviewed.[1]

There is no doubt that during the episodes at Donora and London the death rates mounted. The evidence is clear that certain air pollutants can cause bronchitis. There is abundant evidence that the Los Angeles smog affects the eyes of its citizens, temporarily at least, to the point of distraction. Mills[2] said, "The present report shows a clearly significant association between Los Angeles smogs and rises in day-by-day respiratory and cardiac deaths in the exposed population." Evidence is accumulating which suggests that air pollution may be causally involved in asthma, emphysema, and lung cancer. Stocks and Campbell estimated that about 35% of deaths from cancer of the lung in the Liverpool area result from air pollution. Mancuso maintained that air pollution represents a highly probable and important factor in the excess of lung cancer in urban areas. Kotin said that atmospheric pollution, both epidemiologically and in the laboratory, must be regarded as one of multiple factors operating in combination to result in lung cancer.

In a symposium in San Francisco, January 16-18, 1960, sponsored by the University of California School of Medicine and Continuing Education in Medicine and the Health Sciences, University of California, Northern Area, David F. Eastcott, M.D., formerly assistant director, National Institute of Health of New Zealand, presented a paper entitled "Other Airborne Factors in Cancer." He said that immigrants to New Zealand from highly industrialized Britain run a risk of lung cancer 30% greater than persons born in New Zealand of the same stock and way of life. If they are more than 30 years of age on coming to New Zealand, their risk is 75% greater. This can only be explained logically, Dr. Eastcott said, in terms of atmospheric environment, and it is significant that the effects of the British environment are felt many years after the person has left Britain to live in the cleaner New Zealand environment. Work done on lung cancer and bronchitis in Britain is consonant with this interpretation and renders it difficult to uphold any other.

Public Health Service Surgeon General Burney in his welcoming address before the National Conference on Air Pollution said that "investigators are finding a definite association between community air pollution and high mortality rates due to cancer of the respiratory tract, including the lungs, cancer of the stomach and esophagus, and arteriosclerotic heart disease."

There is another part to this drab picture, that of the cost in damaged crops and livestock, damaged buildings, lowered real estate values, and excessive laundry, cleaning, and paint bills. And how about the housewives who scrub and scrub to keep the grime away? While no one knows the cost of air pollution in these areas, estimates place it at billions of dollars a year.

This enormous, complex problem will probably get worse before it gets better, since our cities and total industrial output are becoming larger each year. Dyktor,[3] Commissioner of the Division of Air Pollution Control of Cleveland, has said that complete elimination of air pollution is not economically attainable. The aroused public will have its say about that. Already the 84th Congress of the United States has responded by enacting a law which directs the Public Health Service to conduct research and provide technical services to state and local governments and private agencies. The goal of this program is to determine the conditions under which toxic substances in the air affect human health, and the measures which must be applied to prevent adverse effects. A National Air Sampling Network is at work and 180 cities and 51 nonurban areas have sampling stations. Each state has at least one urban and one nonurban sampling station and seven states have their own sampling networks.

The Sanitary Engineering Centers in Cincinnati and in the field offer training courses, and more than 900 persons took part in them during fiscal year 1958. At least 14 universities were offering graduate courses in subjects related to air pollution as of November, 1959. Cities are banding together to form country-wide air-pollution control districts. Thus, a good start has been made. We may be surprised at what can be done if everybody,

MEDICAL NEWS

GEORGIA

Annual Session in Columbus.—The Medical Association of Georgia will hold its annual meeting May 1-4 at the Municipal Auditorium, Columbus, under the presidency of Dr. Luther H. Wolff, Columbus. The program includes the following guest speakers:

Drs. Lenox D. Baker, Durham, N. C.; Owen H. Wangensteen, Minneapolis; Francis Murphey, Memphis, Tenn.; John J. Shea Jr., Memphis; C. Paul Winchell, Minneapolis, Louis P. Britt Jr., Memphis; Edward B. D. Neuhauser, Boston; Lent C. Johnson Jr., Washington, D. C.; Curtis J. Lund, Rochester, N. Y.; Henry K. U. Beecher, Boston; Paul G. Reque, Birmingham, Ala.; Wyland F. Leadbeater, Boston; Harry Prystowsky, Gainesville, Fla.; Luther A. Longino, Boston; Leslie V. Dill, Washington, D. C.; George J. Curry, Flint, Mich.; and Franklin B. Peck Sr., Indianapolis.

A joint section meeting on radiology, pediatrics, orthopedics, surgery, and neurological surgery will follow the business session, May 1. A general practice day May 2 will include a panel discussion on traffic injuries moderated by Dr. Julian K. Quattlebaum, Savannah. Governor S. Ernest Vandiver will present "Your State Government and the Medical Profession" following the Dr. A. C. Hobbs Memorial Concert by the Columbus City Symphony Orchestra, the evening of May 1. A ladies' program is arranged. For information, write Mr. Milton D. Krueger, 938 Peachtree St., N. E., Atlanta 9, Ga., Executive Secretary.

HAWAII

Health Department Changes.—Dr. Richard K. C. Lee, Honolulu, was sworn in as director of health, Hawaii State Health Department, Jan. 20, following creation of the new department of health provided by state reorganization. The responsibility for decision making rests solely with the director of health, as the Board of Health, to be appointed soon, will be an advisory board only. The Territorial Hospital (for the mentally ill) and Waimano Home (for the mentally retarded) formerly in the Department of Institutions, became part of the State Health Department. Also, the dental hygiene section of the Department of Public Instruction was transferred to the health department. With this change, the staff of employees more than doubles, from 650 to over 1,500. Medical care for the indigent and medically indigent was transferred to the new Department of Social Services.

ILLINOIS

Dr. Smiley Honored.—Dr. Dean F. Smiley, Evanston, secretary, Association of American Medical Colleges, was honored April 3 by fellow alumni of the Cornell University Medical College when he received the 12th annual alumnus award for his "outstanding contributions to medicine." Dr. Smiley was honored for his work with the Association of American Medical Colleges, with the Educational Council for Foreign Medical Graduates (as executive director), and with Cornell University, where he taught for 22 years. Dr. Smiley has been secretary of the A. A. M. C. since 1948 and has served as consultant on health and fitness to the American Medical Association. Since 1951 he has edited the *Journal of Medical Education.*

Annual State Meeting.—The Illinois State Medical Society will hold its 120th annual meeting in the Hotel Sherman, Chicago, May 24-27. The scientific program will consist of formal papers, panels, symposiums, exhibits, motion pictures, and a closed television demonstration. The first memorial lecture in honor of Dr. Harold M. Camp, who served as the society's secretary for 35 years, will be presented by Dr. Michael E. DeBakey, Houston, Texas, professor of surgery, Baylor University College of Medicine, entitled "Surgical Patterns of Atherosclerosis." The annual "Orations" speakers will be (surgery) Dr. Willis J. Potts, Chicago, professor of surgery, Northwestern University Medical School, "Changing Aspects of Pediatric Surgery"; and (medicine) Dr. Joseph B. Kirsner, Chicago, professor of medicine, University of Chicago School of Medicine, "The Treatment of the 'Untreatable' Patient." Section meetings on allergy, anesthesiology, cardiovascular disease, dermatology, EENT, medicine, obstetrics and gynecology, pathology, pediatrics, preventive medicine and public health, radiology, and surgery are scheduled. For information, write Dr. George F. Lull, Secretary, Illinois State Medical Society, 360 N. Michigan Ave., Chicago 1.

Chicago

Annual Lecture Given.—The 17th annual D. J. Davis Lecture on Medical History, "Mediaeval Medicine: Pre-Christian Fabric and Present Day Remnants," was given by Barry J. Anson, Ph.D., of the department of anatomy, Northwestern University Medical School, March 13, at the University of Illinois College of Medicine. This lecture series was

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Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

THE PRESIDENT'S PAGE

A MONTHLY MESSAGE

I have received a reply from Mr. George Meany in answer to my demand for an apology and retraction from the AFL-CIO for untrue and scurrilous charges made against the American Medical Association and its members by COPE, the union's political education arm.

In his reply Mr. Meany implies that COPE's attack was based on A. M. A. actions in areas "outside its professional competence." I have answered this implication by stating emphatically that the COPE allegations specifically involved health and medical matters. Here are the areas concerned; you may decide for yourself:

"The reporting of tuberculosis cases to a public authority; opposition to the National Tuberculosis Act; compulsory vaccination for smallpox; immunization against diphtheria; infant and maternal death prevention; venereal disease clinics; diagnostic centers for tuberculosis and cancer; blood banks; medical education; health insurance; school health; public health units, and Medicare."

To suggest that the A. M. A. is not competent to act or comment on these subjects is like claiming that the AFL-CIO is not competent to discuss the fields of automation, the minimum wage, the Taft-Hartley act, labor racketeering, and job discrimination. So, contrary to Mr. Meany's implication, the COPE allegations did deal with matters that the A. M. A. not only had a right and a responsibility to comment on, but also had competence in.

Mr. Meany's letter also begs the main issue: Were COPE's charges true or false?

As I reported to you last month, I included in my letter to Mr. Meany the A. M. A.'s refutations—carefully documented—to all 15 COPE allegations. My letter showed the charges to be untrue.

Mr. Meany answered that "we have re-examined this record and find no basis for retraction." However, COPE originally recited no "record" in its attack on the A. M. A. but simply listed a series of unsupported allegations. Mr. Meany in his letter to me offered no "record" and no supporting evidence.

Therefore, in light of his refusal, or inability, to document his case against the A. M. A. I stand on our refutations of the scurrilous COPE charges. And I contend that the COPE allegations were indeed untrue, and that I was correct—and still am—in demanding an apology and a retraction for the distortions of the truth made by COPE.

Finally, I have told Mr. Meany in my reply that physicians are entitled to express their opinion on any matter of government, just as are all other citizens of the United States. The men and women of labor have this identical right and exercise it freely. Why then should the right of a physician to speak, as a citizen, on matters affecting him as a citizen be denied? Why should the right of organized medicine to speak on matters affecting the health of the American people be denied?

The American Medical Association does not claim that the AFL-CIO assumes an omniscience in fields outside its professional competence and presumes to tell the American people "what is good and what is bad" when it beats the drums for Forand-type legislation.

The American Medical Association does ask, again, that the AFL-CIO's political arm, COPE, put aside the weapons of untruth and base its efforts on appeals to logic, instead of appeals to emotion and bias.

Louis M. Orr, M.D.
Orlando, Fla.

Clinic staff members will present a series of six "dry clinics" on pertinent topics in the Mayo Civic Auditorium on Wednesday, May 25. For information, write the Committee on Scientific Assembly, Minnesota State Medical Association, 496 Lowry Medical Arts Building, St. Paul 2, Minn.

MISSOURI

Plan Overnight Housing for Out-Patients.—The University of Missouri Medical Center will provide overnight housing facilities soon for use of out-of-town indigent patients of the out-patient clinic, Dr. Vernon E. Wilson, dean of the school of medicine and director of the medical center, announced. The housing facilities will apply to those out-patients who come from considerable distances and lack funds to care for themselves. The overnight housing will be provided during the time such patients receive treatment at the clinic. A building known as Temporary Dormitory 4, will be used for the facilities. Limited food services in the medical center cafeteria will be provided. A member of the university hospital personnel will be on duty at the overnight facility at all times. No medical treatment will be given in the dormitory.

NEW JERSEY

Dr. Read Receives Honorary Degree.—Dr. Hilton S. Read, Atlantic City, director of the Ventnor Diagnostic Center and executive director of the Ventnor Foundation (which since 1951 has brought 463 selected recent graduates of medicine from Western Germany, Austria, and Switzerland medical universities to the United States for one year internship) was awarded an honorary degree of doctor of medicine by the University of Cologne, with a citation which reads, in part, as follows:

> "The Medical Faculty of the University of Cologne . . . decided unanimously to confer upon you the honorary degree of Doctor of Medicine. This is a high honor very rarely bestowed on anyone by the universities of our country. In making this presentation we express our gratitude to you for your efforts in establishing contacts in the field of medicine and also human bonds between your country and Germany. . . . You have made it possible for many young doctors to get to know your great country and its excellent medical institutions and to have thorough contact with the progressive ideas of your countrymen . . ."

Symposium on Diabetes.—The New Jersey State Department of Health in cooperation with the New Jersey Diabetes Association will present its second annual spring symposium, "Pre-Diabetes and Diabetes in Pregnancy," at the Princeton Inn, Princeton, May 11. The program includes the following papers:

Pre-Diabetes in Pregnancy, Dr. Hugh L. C. Wilkerson, Brighton, Mass.
Medical Management of Diabetes in Pregnancy, Dr. Priscilla White, Boston.
Obstetrical Management of the Pregnant Diabetic, Dr. Alan F. Guttmacher, New York City.

A panel discussion will be moderated by Dr. Karl E. Paschkis, associate professor of medicine, Jefferson Medical College, Philadelphia. Members of the American Academy of General Practice will receive three hours credit under category 2 for attendance. For information, write Dr. Arthur Krosnick, Coordinator, Diabetes Control Program, New Jersey Department of Health, Trenton 25, N. J.

NEW YORK

Study Laws for Committing Mental Patients.—Dr. Paul H. Hoch, state commissioner of mental hygiene, on March 28 commended the Association of the Bar of the City of New York for the establishment of a special committee to examine and evaluate existing laws, administrative regulations, and practices governing admission and release of mental patients in New York State hospitals. "The department is particularly interested in voluntary admissions and admissions based on physicians' certificates," Dr. Hoch said. "In Great Britain . . . certification is used very sparingly and more patients are being admitted on a non-judicial basis." In addition to Commissioner Hoch, the Department of Mental Hygiene will be represented on the committee by Dr. Arthur W. Pense, Albany, deputy commissioner of mental hygiene, and Dr. Francis J. O'Neill, director of Central Islip State Hospital, Dr. Benjamin Apfelberg, associate director, psychiatric division, Bellevue Hospital, New York City, and Dr. Harold C. Miles, director of the Monroe County Community Mental Health Services, will serve as consultants.

New York City

Annual Lecture.—The ninth annual Ira I. Kaplan Lecture will be held Thursday, May 26, 5:30 p. m., in the main auditorium, Alumni Hall, New York University School of Medicine, 550 First Avenue at 31st Street. The lecturer will be Dr. Sidney Farber, professor of pathology, Harvard Medical School, Boston, and director of research, Children's Cancer Research Foundation, who will present "Biological and Therapeutic Considerations of Cancer in Early Life."

Change Names of Medical Center and School.—By joint action, the board of trustees of New York University and the NYU Medical Center Board approved on March 28 changes in the following official names, effective immediately: (1) the name of the medical center is now New York University Medical Center (formerly New York University-Bellevue Medical Center); (2) the name of the College of Medicine has been changed to New York University School of Medicine (formerly New established by the associates and friends of Dr. Davis on his retirement as dean of the College of Medicine in 1943.

Personal.—Dr. Gilbeart H. Collings Jr. was appointed medical director of Standard Oil Company, succeeding Dr. Bryce B. Reeve, who retired. Dr. Collings is former director of the American Industrial Hygiene Association and is a medical advisor to the National Safety Council.——Dr. Sidney R. Bazell was named president of the board of trustees of the Chicago Medical School Medical Research Foundation. Other new members are Dr. William W. Patrick (secretary) and David Borowitz, businessman.

Dr. Coggeshall Appointed University Vice-President.—The appointment of Dr. Lowell T. Coggeshall as a vice-president of the University of Chicago was announced April 7. He has been dean of the division of biological sciences at the university since 1947. In his new position, Dr. Coggeshall primarily will be responsible for the development of medical research programs and facilities at the university. In addition, he will seek to build up resources for the general activities of the biological sciences division, one of the largest in the university. Dr. Coggeshall will continue to serve as dean until a successor is appointed.

University News.—Dr. Robert D. Moore, Kankakee, was appointed chief of the orthopedic section of the department of surgery, University of Chicago, The School of Medicine, effective July 1, when he also will become professor of surgery. Dr. Moore succeeds Dr. C. Howard Hatcher, who resigned. Dr. Moore had previously been a member of the University of Chicago faculty, most recently as assistant professor of surgery, 1946-1948.——Dr. Hilger P. Jenkins was appointed professor of surgery at the University of Chicago, The School of Medicine. Dr. Jenkins, a member of the University of Chicago faculty from 1930 to 1947, served on the staff of the University of Illinois College of Medicine from 1947 through 1959. He is past-president of the Chicago Surgical Society and the Central Surgical Association and a past-member of the executive committee of the board of governors of the American College of Surgeons.

MASSACHUSETTS

Dr. Soutter Named Dean.—Dr. Lamar Soutter, of Dedham, professor of surgery at Boston University's School of Medicine and acting dean since September, was appointed dean of the School of Medicine. Dr. Soutter received his A.B. and M.D. degrees from Harvard and later began the practice of surgery and started the blood bank at the Massachusetts General Hospital. In 1952, he was appointed to the faculty of Boston University and to the staff of the Massachusetts Memorial Hospitals and the Boston City Hospital. Dr. Soutter served as associate dean of the university's School of Medicine since 1955. He is vice-president of the Suffolk District Medical Society.

MICHIGAN

Plan Medical Program for Special Students.—The University of Michigan Medical School, Ann Arbor, will launch a Special Studies program for certain entering students next fall. Dr. William N. Hubbard Jr., dean, said about 10% of the 200 students entering the Medical School will be invited to participate. They will be chosen on the basis of motivation, special interests in medicine, and exceptional intellectual capacity. Dr. John M. Weller, associate professor of internal medicine was named coordinator of the program. The Special Studies plan is an attempt to provide a more challenging medical education for the superior students. Groundwork for the program was carried out by a faculty committee headed by Halvor N. Christensen, Ph.D., chairman, department of biological chemistry. Dr. Weller said the committee's recommendations for Special Studies included: seminars, research reports, and guest lectures; close tutorial supervision of the student's work; individual research programs, and other "special learning and investigative opportunities." The committee recommended partial financial support for students in the program through scholarships and fellowships, and they suggested that "the students might substitute special work or passage of an examination for attendance at regular exercises." At the same time, every student must still meet all the usual requirements for graduation.

MINNESOTA

State Meeting in Rochester.—The committee on scientific assembly, Minnesota State Medical Association, announced that the general scientific program highlights of its 107th annual meeting will be held May 23-25 in the Mayo Civic Auditorium, Rochester. A day of symposiums on rheumatic heart disease and diseases of the lung is scheduled for Monday, May 23. The final scientific session scheduled for that day will feature a clinical-pathological conference, "Diseases of the Chest," with Dr. Herbert W. Schmidt, of Rochester, as moderator. Scientific sessions on Tuesday, May 24, will be devoted to cancer. A symposium, "Cancer Detection for Practicing Physicians," has been set for 9 a. m. Dr. Joseph H. Ogura, St. Louis, will give the Minnesota Academy of Ophthalmology and Otolaryngology Lecture, "Cancer of the Throat," at 11 a. m. Included in the Tuesday program will be two symposiums, on cancer treatment and management of the far-advanced cancer patient. Mayo

GENERAL

Meeting of Southern Railway Surgeons.—On May 9-10, the Association of Surgeons of the Southern Railway System will meet in Charleston, S. C., under the presidency of Dr. Sam O. Black Jr., Spartanburg, S. C., who will open the scientific sessions with "Ligament Injuries of the Knee and Ankle" as the presidential address. A total of 23 papers is scheduled for presentation. On the morning of May 10, a tour will be conducted to the United States Naval Base, where program participants will be introduced to the medical aspects of the Nuclear Power Overhaul Program. For information, write Dr. Rudolph M. Landry, 707 Walnut St., Chattanooga 2, Tenn., Program Chairman.

Premedical Society Meeting Held.—Alpha Epsilon Delta, national premedical honor society, held its 13th national convention at the University of Louisville (Ky.) School of Medicine, April 7-9, with the Kentucky Alpha Chapter as host to the 74 chapters in colleges throughout the United States and Canada. Dr. Ward Darley, Evanston, Ill., executive director, Association of American Medical Colleges, was the convention banquet speaker. Other speakers included Dr. William K. Keller, professor of psychiatry, University of Louisville School of Medicine; Dr. Walter S. Wiggins, Chicago, Secretary, Council on Medical Education and Hospitals, American Medical Association; and Maynard K. Hine, D.D.S., dean, Indiana University School of Dentistry.

Meeting on Thoracic Surgery.—The 40th annual meeting of the American Association for Thoracic Surgery, will be held May 11-13 in Miami Beach, Fla., with headquarters at the Deauville Hotel, under the presidency of Dr. William E. Adams, Chicago. A total of 42 papers is scheduled for the scientific program, and will include "Lung Abscess in Japan" by Dr. Kingo Shinoi, Tokyo, Japan. A thoracic surgery forum is scheduled for May 12, the afternoon of which will include an address by the guest speaker, Dr. Alfonso Topete, Guadalajara, Mexico, chairman, department of surgery, University of Guadalajara, presenting "New Findings in the Coronary-Encephalic Perfusion in Depressive Surgical Cases." A banquet is planned for the evening of May 12. For information, write Dr. Hiram T. Langston, 7730 Carondelet Ave., St. Louis 5, Secretary.

Psychiatrists Meeting in Atlantic City.—The American Psychiatric Association will hold its 116th annual meeting at the Hotel Traymore, Atlantic City, N. J., May 9-13 under the presidency of Dr. William Malamud, Boston. Section meetings are planned on the following: psychoanalysis, psychophysiological research, clinical psychiatry, the mental hospital and social psychiatry, research, mental hospitals, follow-up studies, child psychiatry, forensic psychiatry, schizophrenia, psychotherapy, convulsive disorders and brain function, education, suicide, and other topics. The morning of May 12, Sir Aubrey J. Lewis, M.D., professor of psychiatry, University of London, will present the Adolf Meyer Lecture, "The Study of Defect." Roundtable discussions are planned for May 10 and 12. Among the papers to be presented is "Evaluation of Emotional Disturbance in 403 Israeli Kibbutz Children," by Dr. Mordecai Kaffman, Jerusalem, Israel. Dr. Malamud will give the presidential address following the election of new members the morning of May 9. For information, write Dr. C. H. Hardin Branch, 156 Westminster Ave., Salt Lake City 15, Utah, Secretary.

Annual Meeting on Mental Deficiency.—The 84th annual meeting of the American Association on Mental Deficiency will meet May 17-21 at the Lord Baltimore Hotel, Baltimore. The program includes the following panel discussions:

A Look at Maryland's Program for the Mentally Retarded—Are Its Assets and Liabilities Specific to the State or Are They Universal?
Research in Education.
The Relationships Between Administrators, Supervisors, and Teachers for Better Curriculum Practices.
Community Programs for Mentally Retarded.
Education and National Association for Retarded Children.

Section meetings are planned on education, social work, medicine, psychology, and administration. On May 18, 8 p. m., Secretary of Health, Education, and Welfare Arthur S. Flemming will present "Mental Deficiency as Viewed by the State Department." The president's dinner will be held May 20, 7 p. m. Registration fee for members is $1 and for nonmembers, $2. For information, write Mr. Neil A. Dayton, P. O. Box 51, Mansfield Depot, Conn., Executive Secretary-Treasurer.

Conference of Food and Drug Officials.—Secretary of Health, Education and Welfare Arthur S. Flemming will head the list of speakers at the 64th annual national conference of the Association of Food and Drug Officials of the United States to be held June 5-9 at the Baker Hotel, Dallas, Texas. Mr. Harold Clark, Hartford, Conn., of the Connecticut Food and Drug Commission and president of the association, announced that the conference will hear discussions of the narcotics problems in the various states. Authorities will present papers on current developments in connection with the food additives and color amendments, on means of making safer the use of hazardous substances in homes and in industry, and on problems in regard to the frozen food code. A special event will be the fifth annual presentation of the Harvey W. Wiley

York University College of Medicine). Dr. George E. Armstrong, center director, stated that the center's affiliation with the Bellevue Hospital Center will continue unchanged. It is requested that future use of this institution's title be in accordance with the changes detailed above.

Dr. Wortis Named Dean.—Dr. S. Bernard Wortis, chairman, department of psychiatry and neurology, New York University Medical Center, was named dean of New York University School of Medicine and Post-Graduate Medical School and deputy director of the center, effective April 1. Dr. Wortis, Lucius N. Littauer Professor of Psychiatry and Professor of Neurology, will retain his present departmental and academic appointments. He succeeds Dr. Donal Sheehan, who will continue in his capacity as chairman of the department of anatomy. Under the auspices of the World Health Organization and the Unitarian Service Committee, Dr. Wortis has served on medical teaching missions to Austria, Poland, Finland, and Iran. He was named a member of the Conference on Treatment of Drug Addiction held under the auspices of WHO in Geneva in 1956. He is editor of the "Yearbook of Neurology, Psychiatry and Neurosurgery" and an associate editor of the *Journal of Diseases of the Nervous System* and of the *Journal of Clinical and Experimental Psychopathology*.

OHIO

Memorial Planned for Dr. Mitchell.—A memorial to Dr. A. Graeme Mitchell will be established at the University of Cincinnati through the efforts of pediatricians who studied under the distinguished authority. Dr. Mitchell, who died in 1941 at the age of 52, was professor of pediatrics at the University of Cincinnati College of Medicine, medical director and chief of staff of Children's Hospital, director of the Children's Hospital Research Foundation, and director of pediatrics and contagious diseases at Cincinnati General Hospital. Physicians who were residents during Dr. Mitchell's tenure at Children's Hospital have begun a campaign to raise funds for a permanent memorial to Dr. Mitchell. First stage will be a lecture series at the university devoted to Dr. Mitchell's major talents, including his avocations of writing and art. Dr. Carl J. Ochs, of Cincinnati, is chairman of the committee.

OREGON

Research Fund Honors Senator Neuberger.—The Senator Richard L. Neuberger Fund for Medical Education and Research at the University of Oregon Medical School was established at the request of Mrs. Neuberger in memory of her husband, Oregon's junior senator, who died in March. Senator Neuberger was instrumental in obtaining matching funds from the National Institutes of Health for the $2,500,000 Medical Research Building to be built at the Medical School and often spoke of the programs underway at the university's medical school from the floor of the U. S. Senate.

PENNSYLVANIA

Meeting on Rehabilitation in Williamsport.—The Pennsylvania Academy of Physical Medicine and Rehabilitation will meet May 21 at the Divine Providence Hospital, Williamsport, at 1:30 p. m. The program is as follows:

Physiological Price of Pain Relief, Dr. J. Donald Wentzler, Williamsport.
Photosensitive Skin Diseases, Clinical Considerations, Dr. William T. Ford, Williamsport.
Rehabilitation of the Mentally Retarded, Dr. Max C. Miller, Williamsport.
Recent Orthopedic Procedures for the Unstable Hip, Dr. Francis V. Costello, Williamsport.

For information write, Dr. J. Murl Johnston, 694 Washington Rd., Pittsburgh 28, Secretary-Treasurer.

Philadelphia

Undergraduates Present Research Papers.—Students at the University of Pennsylvania School of Medicine presented 16 scientific papers on results of original student research April 7 at the 52nd Undergraduate Medical Association Day. Ten additional papers were noted by title. This annual all-day student research presentation was first launched in 1908, when Dr. O. H. Perry Pepper, Villanova, emeritus professor of medicine, was a student and president of the Undergraduate Medical Association. Increasing emphasis on research has led to similar programs in medical schools throughout the country. In addition to the student research papers, addresses were given by two guest speakers: Dr. Raymond D. Adams, professor of neuropathology Harvard University, Boston, who presented "Diptheritic Paralyses"; and Dr. Ivan L. Bennett Jr., professor of pathology, Johns Hopkins University School of Medicine, Baltimore, who gave "Pathology of Fever."

WASHINGTON

Joint Allergy Meeting.—The annual meeting of the Washington State Allergy Society will be held jointly this year with the Oregon State Allergy Society as the Northwest Allergy Forum May 14 at the Washington Athletic Club, Seattle. The guest speaker will be Dr. Albert H. Rowe, of Oakland, Calif. The current officers of the Washington State Allergy Society are president, Dr. Norman W. Clein, Seattle; vice-president, Dr. Robert F. E. Stier, Spokane; secretary-treasurer, Dr. James W. Georges, 1140-44 Medical-Dental Bldg., 509 Olive Way, Seattle 1.

EXAMINATIONS AND LICENSURE

EDUCATIONAL COUNCIL FOR FOREIGN MEDICAL GRADUATES, INC.

Educational Council for Foreign Medical Graduates: Stations around the world. Sept. 21, 1960. Exec. Director, Dr. Dean F. Smiley, 1710 Orrington Ave., Evanston, Ill.

NATIONAL BOARD OF MEDICAL EXAMINERS

National Board of Medical Examiners: Part I, Various Cities, June 21-22 and Sept. 7-8. Part II. Applications must be received at least six weeks before the date of the examination. Exec. Sec., Dr. John P. Hubbard, 133 South 36th St., Philadelphia.

BOARDS OF MEDICAL EXAMINERS

Alabama: _Examination._ Montgomery, June 21-23. Sec., Dr. D. G. Gill, State Office Bldg., Montgomery.

Alaska:* On application in Anchorage or Fairbanks. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

Arkansas:* _Examination and Reciprocity._ Little Rock, June 9-10 Sec., Dr. Joe Verser, Harrisburg.

California: _Written._ San Francisco, June 20-23; Los Angeles, Aug. 22-25 and Sacramento, Oct. 17-20. _Oral and Clinical._ Los Angeles, San Francisco, June 19; Los Angeles, Aug. 21, and Los Angeles, Nov. 29. _Oral for Reciprocity Applicants._ San Francisco, June 18; Los Angeles, Aug. 20 and Nov. 19. Sec., Dr. Louis E. Jones, Room 536, 1020 N Street, Sacramento.

Canal Zone: On Application. Acting Sec., Dr. B. K. Levin, Health Bureau, Balboa Heights.

Colorado:* _Examination._ Denver, June 14-15. Sec., Dr. John B. Farley, 1612 Tremont Place, Denver 2.

Delaware: _Examination and Endorsement._ Dover, June 12-14 and July 21. Sec., Dr. Joseph S. McDaniel, Professional Bldg., Dover.

District of Columbia:* _Examination._ Washington, June 13-14. Deputy Director, Mr. Paul Foley, Department of Occupations and Professions, 1740 Massachusetts Ave., N.W., Washington 6.

Florida:* _Examination._ Miami Beach, June 19-21. Sec., Dr. Homer L. Pearson, 901 N.W. 17th St., Miami 36.

Georgia: _Examination and Reciprocity._ Atlanta, June. Sec., Mr. Cecil L. Clifton, 224 State Capitol, Atlanta 3.

Guam: _Subject to Call._ Act Sec., Dr. F. L. Conklin, Agana.

Idaho: _Examination and Endorsement._ Boise, July 11-13. Exec. Sec., Mr. Armand L. Bird, 358 Sonna Bldg., Boise.

Indiana: _Examination._ Indianapolis, June 22-24. _Reciprocity._ Indianapolis, fourth Wednesday of each month. Ex. Sec., Miss Ruth V. Kirk, 538 K. of P. Bldg., Indianapolis.

Kentucky: _Examination._ Louisville, June 6-7. Sec., Dr. Russell E. Teague, 620 South Third St., Louisville 2.

Louisiana: _Examination and Reciprocity._ New Orleans, June 9-11. Sec., Dr. Edwin H. Lawson, 930 Hibernia Bank Bldg., New Orleans 12.

Maryland: _Examination._ Baltimore, June 15-18. Sec., Dr. Frank K. Morris, 1215 Cathedral St., Baltimore 1.

Michigan:* _Examination._ Ann Arbor and Detroit, June 6-8. Sec., Dr. E. C. Swanson, 118 Stevens T Mason Bldg., Lansing.

Mississippi: _Examination._ Jackson, June 20-21; _Reciprocity,_ Jackson, June 16. Sec., Dr. A. L. Gray, Old Capitol, Jackson 13.

Missouri: _Examination._ St. Louis, May 27-28. Exec. Sec., Mr. John A. Hailey, State Capitol Bldg., P. O. Box 4, Jefferson City.

Nebraska:* _Examination._ Omaha, June 13-15, 1960. Dir., Bureau of Examining Boards, Room 1009, State Capitol Bldg., Lincoln 9.

Nevada: _Examination and Reciprocity._ Reno, June 8, Sept. 7 and Dec. 7. Sec., Dr. G. H. Ross, 112 North Curry St., Carson City.

New Mexico:* _Examination and Reciprocity._ Santa Fe, May 16-17. Sec., Dr. R. C. Derbyshire, 227 East Palace Ave., Santa Fe.

New York: _Examination._ Albany, Buffalo, New York City, Rochester and Syracuse, June 28-July 1. Sec., Dr. Stiles D. Ezell, 23 S. Pearl Street, Albany.

North Carolina: _Endorsement._ Raleigh, May 9. _Examination and Endorsement._ Raleigh, June 20-23. Sec., Dr. Joseph J. Combs, 716 Professional Bldg., Raleigh.

North Dakota: _Examination and Reciprocity._ Grand Forks, July 13-16. Sec., Dr. C. J. Glaspel, Grafton.

Ohio: _Reciprocity._ Columbus, June 17. _Examination._ Columbus, June 16-18. Sec., Dr. H. M. Platter, 21 West Broad St., Columbus 15.

Oklahoma:* _Examination and Endorsement._ Oklahoma City, May 31-June 1. Sec., Dr. E. F. Lester, 813 Braniff Bldg., Oklahoma City.

Oregon:* _Examination._ Portland, July. Exec. Sec., Mr. Howard I. Bobbitt, 609 Failing Bldg., Portland.

Pennsylvania: _Examination._ Philadelphia and Pittsburgh, July 5-7. Sec., Mrs. Margaret G. Steiner, Box 911, Harrisburg.

South Carolina: _Endorsement._ Myrtle Beach, May 17. _Examination._ Columbia, June 28-29. Sec., Dr. Harold E. Jervey, Jr., 1329 Blanding St., Columbia.

Texas:* _Examination and Reciprocity._ Fort Worth, June 20-22. Sec., Dr. M. H. Crabb, 1714 Medical Arts Bldg., Fort Worth 2.

Utah: _Examination._ Salt Lake City, July 6-8. Director, Mr. Frank E. Lees, 324 State Office Bldg., Salt Lake City 1.

Vermont: _Examination and Reciprocity._ Burlington, June 16-18. Sec., Dr. F. J. Lawliss, Richford.

Virgin Islands: _Examination._ Charlotte Amalie, St. Thomas, June 8-9. Sec., Dr. Benjamin A. Nath, Charlotte Amalie, St. Thomas.

Virginia: _Examination and Reciprocity._ Richmond, June 13-17. Address: Board of Medical Examiners, 631 First St. S.W., Roanoke.

West Virginia: _Examination and Reciprocity._ Charleston, April 18. Sec., Dr. Newman H. Dyer, State Office Bldg. No. 3, Charleston 5.

Wyoming: _Examination and Reciprocity._ Cheyenne, June 6. Acting Sec., Dr. Carleton D. Anton, State Office Bldg., Cheyenne.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

Arkansas: _Examination._ Little Rock, April 21-22. Sec., Dr. A. W. Ford, Department of Education, Education Bldg., Little Rock.

District of Columbia: _Examination._ Washington, May 23-24. Deputy Director, Mr. Paul Foley, Department of Occupations and Professions, 1740 Massachusetts Ave., Washington 6.

Florida: _Examination._ Miami, June 4. Sec., Mr. M. W. Emmel, Box 340, Gainesville.

Kansas: _Examination._ Kansas City, June 10-12. Sec., Dr. Leon C. Heckert, Kansas State College, Pittsburg.

Nebraska: _Examination._ Omaha, May 3-4. Sec., Mr. R. K. Kirkman, Room 1009, State Capitol Bldg., Lincoln 9.

South Dakota: _Examination and Reciprocity._ Vermillion, June 10-11. Sec., Dr. Gregg M. Evans, 310 E. 15th St., Yankton.

Washington: _Examination._ Seattle, July 13-14. Administrator, Mr. Thomas A. Carter, Department of Licenses, Capitol Bldg., Olympia.

Wisconsin: _Examination._ Milwaukee, June 4. Sec., Dr. W. H. Barber, 621 Ransom St., Ripon.

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*Basic Science Certificate required.

Award to a food and drug official for "outstanding service, devotion to duty and leadership in his field both locally and nationally." The Association of Food and Drug Officials is the professional society of food and drug enforcement officers in all levels of government—federal, state, and municipal. The host state is represented among the national officers by Secretary-Treasurer J. F. Lakey, Director of the Division of Food and Drugs of the Texas State Department of Health.

Cardiology Meeting in Indianapolis.—The American College of Cardiology will hold its ninth annual convention at the Claypool Hotel, Indianapolis, May 23-28. Dr. Gabriel F. Greco, Ozone Park, N. Y., chairman, publicity committee, announced that the program will present a variety of topics of current interest in cardiology. Dr. Samuel A. Levine, Boston, will deliver the guest lecture, "Some Prevalent Errors in the Practice of Cardiology." A symposium on recent advances in the treatment of congestive heart failure will include topics on physiology, pharmacology, changing mechanisms, fluids, electrolytes, cardiac glycosides, and other measures. Scientific sessions will be devoted to surgical management of coronary artery diseases, with emphasis on criteria for the selection of patients, and availability of surgical methods for the improvement of collateral circulation. A survey of the diagnosis and treatment of congenital heart diseases, with an analysis of diagnostic methods, surgical treatment, and end-results in the cyanotic and acyanotic groups, and panel discussions and scientific exhibits are planned. Fireside conferences will provide for open discussions of current problems in cardiology. Dr. Osler A. Abbott, Atlanta, president of the college, will preside at the sessions. Information on the meeting may be obtained from Dr. Philip Reichert, Executive Director, Empire State Building, New York 1.

International Meeting on Forensic Pathology.—The second International Meeting on Forensic Pathology and Medicine will be held in New York City Sept. 18-21 at the department of forensic medicine, New York University Medical Center, 550 First Ave., New York 16. The meeting will include as part of the ceremonies the dedication of the new building for the office of chief medical examiner of the City of New York. Scientific meetings will be held Sept. 19, 20, and 21. The morning sessions will be devoted to symposiums on problems of education and training in forensic medicine, the role of forensic medicine in the proper administration of justice, and misconceptions in forensic medicine, pathology, toxicology, and serology. The three afternoon sessions will consist of section meetings devoted to forensic pathology and medicine, forensic serology, toxicology, biological aspects of criminalistics, and medical jurisprudence. An excursion to the Lederle Pharmaceutical plant at Pearl Rive N. Y., is planned for Thursday, Sept. 22. Those wh wish to participate in the program are required t submit titles of papers by May 15 accompanied by an abstract of not more than 200 words, with an English translation if possible, which will be included in the official program. Complete manuscripts of papers should be sent in prior to the time of the meeting, preferably before Sept. 1. Registration fee for participants and registrants is $7.50 prior to May 15 and $10 after that date. Fee for guests is $2. For information, write Dr. Milton Helpern, 55 E. End Ave., New York 28.

Clinical Investigators Meeting in Atlantic City.—The annual meeting of the American Society for Clinical Investigation will be held May 1-2 at Haddon Hall, Atlantic City, N. J. Of the 26 papers scheduled on the program, the following will be introduced by members:

On the Role of Virus Sulfhydryl Groups in the Attachment of Enteroviruses to Cells, Lennart Philipson and Dr. Purnell W. Choppin, New York City.

Capacity of Tubercle Bacilli to Assume a Latent State In Vivo, Dr. Robert M. McCune Jr., New York City.

Relationship of Phagocytosis to the Fall in CSF Glucose in Experimental Meningitis, Dr. Robert G. Petersdorf, Baltimore.

Presence of an Altered Amino Acid Sequence in Hgb M (Boston type), Dr. Park S. Gerald, Boston, Dr. Mary L. S. Efron, Brooklyn, and Margaret J. Pease, Boston.

Enzymatic Defect of Orotic Aciduria, Drs. Lloyd H. Smith Jr., Boston, Charles M. Huguley Jr., Atlanta, Ga.

Effect of Wheat Instillation into the Proximal Ileum of Patients with Idiopathic Sprue, Dr. Cyrus E. Rubin, Dr. Lloyd L. Brandborg, Dr. Arnold L. Flick, Cherill Parmentier, Dr. Patricia R. Phelps, and Sally Van Niel, Seattle.

Effect of Cell Structure and Growth Hormone on Protein Synthesis in Striated Muscle, Drs. David M. Kipnis and Eric Reiss, St. Louis.

Over 70 papers are scheduled for presentation at section meetings under the following headings: (1) cardiology, respiration; (2) metabolism; (3) kidney and electrolytes; (4) hematology; (5) infectious disease; and (6) gastrointestinal and liver sectional program. For information, write Dr. Saul J. Farber, New York University College of Medicine, 550 First Ave., New York 16, Secretary.

CORRECTION

Photodynamic Response of a New Tetracycline.—In the Correspondence section of THE JOURNAL, March 12, page 1196, a letter appeared by Dr. Benjamin W. Carey entitled "Photodynamic Response of a New Tetracycline." The word "therapeutic" should be deleted from the last sentence of the first paragraph. The sentence should read as follows: "Extensive pharmacological and laboratory toxicity studies failed to demonstrate any significant difference from the other tetracyclines."

The consultant pathologists will recommend to the civil air surgeon the most effective means by which the tools of this specialized area of medical science can be applied to aircraft accident investigating. The 21 consultant are Drs. Lester Adelson, Cleveland; Frederick Bornstein, El Paso, Texas; Joseph E. Campbell, Chicago; Nicholas Chetta, New Orleans; Theodore J. Curphey, Los Angeles; Joseph H. Davis, Miami, Fla.; Russell S. Fisher, Baltimore; Richard Ford, Boston; Irving I. Goodof, Waterville, Maine; Robert Hausman, San Antonio, Texas; Milton Helpern, New York; Angelo Lapi, Kansas City, Mo.; Charles P. Larson, Tacoma, Wash.; Leo Lowbeer, Tulsa, Okla.; Geoffrey Mann, Richmond, Va.; Donald K. Merkeley, Lewiston, Idaho; William J. Reals, Wichita, Kan.; Joseph W. Spelman, Philadelphia: Vernie A. Stembridge, Dallas, Texas; B. C. Willard, Orlando, Fla.; and Edward S. Zawadski, Detroit.

Dr. Wentz Appointed.—In another step to carry out its many-faceted research activities, the office of the civil air surgeon named Dr. Arthur E. Wentz, a neurologist, as head of the clinical medical research branch. He will be in charge of the program to develop laboratory techniques and procedures that will permit more accurate detection of cardiovascular, respiratory, neurological, and other diseases. The early detection of degenerative diseases in the aging pilot will be emphasized.

FOOD AND DRUG ADMINISTRATION

Drug and Device Seizures.—Dandelion root and slippery elm bark were separately promoted in so-called "food supplements" offered for insomnia, peptic ulcers, colitis, frayed nerves, digestive disorders, dysentery, urinary troubles, elimination of toxic impurities from the blood, and improvement of the eyes and complexion. These products consisted of powdered and liquid extracts to be added to milk and water and served as hot drinks for infants, teen-agers, and invalids. Experts testified that "roast dandelion," "slippery elm food," and similar products were offered on the basis of false representations that commonly available foods will not meet the nutritional needs of the average person. For health and pocketbook protection, consumers should rely on competent medical advice to determine what, if any, supplementation of the diet may be required in the management of disease conditions.

A nonprescription cough preparation for children was claimed to be effective against coughs due to viral and bacterial infections, tonsilitis, laryngitis, tracheitis, and bronchitis. In addition to alleging that the product is not effective for these conditions, the government charged that the label did not warn that persons with a high fever or persistent cough should not take this medicament unless directed by a physician and did not caution against its use without medical supervision by children under 6 years of age and elderly persons.

Also alleged to be misbranded were six makes of capsules offered for weight reduction on the basis that they contained an alleged "appetite suppressant," phenylpropanolamine hydrochloride, which is not effective for controlling the appetite.

Drug Testing Laboratory Supplied False Data.—By supplying false analytic data indicating proper composition of prescription drugs for treating heart disease, high blood pressure, and other serious conditions, an independent testing laboratory (Wyanel Laboratories, Philadelphia) caused the small drug manufacturers it served to make illegal shipments of low-strength products and thus to endanger the health of persons relying on these drugs. Investigation disclosed that no analytic work had been done for many of the reports and that these reports were entirely fictitious.

It took nearly four years to develop sufficient evidence to prosecute the laboratory and its president, Eugene Cohen. The firm claimed to offer complete drug control services, including chemical, bacteriological, and animal testing, to small drug firms, but inspectors found that the firm lacked the facilities and personnel to perform the work. After indictment, it was learned that the corporate status of the Wyanel firm was fictitious, since the firm had never been incorporated. The Harvey-Pittenger Company had been trading as Wyanel Laboratories. The court fined the company $25 and Cohen $1,000. In addition, Cohen was given a one-year suspended jail sentence and placed on probation for three years.

Industry Granted Hearing on Colors Delisting.—A hearing on the order removing 14 colors from the list of colors that may be used in lipsticks ended on March 2. The issues on which testimony was taken at the hearing were (1) whether the government's test results on colors constituted an adequate scientific basis for the conclusion that the colors were not harmless; and (2) whether five colors which had not been tested were sufficiently related chemically to the tested colors to warrant their inclusion in the order.

The government testified in substance that the colors were found toxic to rats at the levels fed and are, therefore, not harmless colors. While agreeing to this fact, the industry witnesses contended that the concept of harmless or harmful could only be applied to the amount of lipstick color that normally gets into the stomach, and this was insignificant compared to the amounts fed the test animals. The government took the position that this was a valid argument for a permitted safe use based on a tolerance, but the law does not provide for limits on amounts used.

GOVERNMENT SERVICES

ARMY

Dr. John B. Youmans Honored.—Dr. John B. Youmans, technical director of research to the office of the surgeon general, will be awarded the Groedel Medal, the highest award of the American College of Cardiology, on May 27, at the meeting of the American College of Cardiology in Indianapolis. At this time he will present an address entitled "The Humanities in Medicine," an obligation incurred by those who receive the medal struck in honor of Franz M. Groedel (1881-1951), the founder and first president of the College of Cardiology. As technical director of research in the Army's medical research and development command, Dr. Youmans provides technical guidance in the making and executing of a balanced research and development program in medical, dental, veterinary, and allied sciences to meet the present and future needs of the Army.

PUBLIC HEALTH SERVICE

American-Soviet Meeting on Poliomyelitis.—Four American scientists have been designated to represent the United States at a joint American-Soviet meeting on poliomyelitis to be held in the Soviet Union in May. A similar joint meeting will be held in the United States next year. The formal invitation to send an American delegation to the meeting was extended by the Minister of Health of the Union of Soviet Socialist Republics, in accordance with the U. S.-U. S. S. R. exchange agreement of Nov. 21, 1959. The mission is the first to take place under the agreement, which, in addition to providing for joint meetings on poliomyelitis, cancer, and heart disease, calls for exchange missions between the two countries on scientific matters and authorizes the surgeon general of the Public Health Service and the Soviet Minister of Health to develop cooperative projects in scientific and medical areas of joint interest.

Personal representative of the surgeon general and chairman of the United States delegation will be Dr. David E. Price, assistant surgeon general. The other members will be Dr. Roderick Murray, of the National Institutes of Health; Dr. Alexander Langmuir, of the Communicable Disease Center, Atlanta, Ga.; and Dr. Albert Sabin of Children's Hospital, Research Foundation, Cincinnati. Additional members of the delegation will be announced.

Retirement of Dr. Lillie.—Dr. Ralph D. Lillie, after 35 years of research at the National Institutes of Health, Bethesda, Md., retired as a medical director of the Public Health Services Commissioned Officers Corps. At the time of his retirement he had served for six years as chief of the laboratory of pathology and histochemistry, National Institute of Arthritis and Metabolic Diseases. He will continue his research with the department of pathology at the Louisiana State University School of Medicine.

Personal.—Dr. Charles R. Mallary was appointed deputy chief of the bureau of medical services effective April 15. Dr. Mallary, whose new assignment carries the rank of assistant surgeon general, is currently medical officer in charge of the Public Health Service Indian health area, in Albuquerque, N. Mex. He will succeed Dr. Arnold B. Kurlander, recently assigned to the surgeon general's office as assistant surgeon general.——Dr. Anthony R. Curreri, professor of surgery at the University of Wisconsin Medical School and director of the University's Cancer Research Hospital, was appointed a member of the National Advisory Cancer Council. His council membership runs from Jan. 1, 1960, until Sept. 30, 1962.

FEDERAL AVIATION AGENCY

Consultant Pathologists.—The federal aviation agency has appointed 21 of the country's leading forensic pathologists as consultants to determine to what extent human factors may be related to aircraft accidents. Establishment of this nationwide system of consultants augments an already existing program to provide for the investigation of fatal accidents. Participation of the pathologists will supplement the work of the office of the civil air surgeon which, with the assistance of pathologists from the Armed Forces Institute of Pathology, has been functioning since last September. The investigation of fatal accidents is performed by the Civil Aeronautics Board, which has legal responsibility to determine probable cause. The medical phase of these investigations is carried out within the framework of the human factors team established by the board.

Under the program, the pathologist located nearest to an accident will visit the scene as soon as possible. An on-the-spot inspection and other studies performed in cooperation with local authorities will attempt to determine any elements involving human factors. These would include a study of possible medical factors involving aircrew personnel which may have contributed to the accident; correlation of the pattern of injury and death with the nature of impact forces, to evaluate the adequacy of aircraft safety provisions; a study of the pattern of injury and death to determine the sequence of events which led up to the accident; and general medical data applicable to current safety rules and regulations of the federal aviation agency. This approach has provided invaluable information in recent accident investigations.

of the Association for Research in Ophthalmology; fellow of the American College of Surgeons; veteran of World War I; served on the faculty of his alma mater; consultant, Prospect Heights Hospital, Brooklyn; associated with the Bird S. Coler Memorial Hospital and Home, Metropolitan Hospital, and Flower and Fifth Avenue Hospitals; died in the Columbia-Presbyterian Medical Center Feb. 12, aged 68.

Tyler, Earl Runyon Ⓜ Durham, N. C.; Jefferson Medical College of Philadelphia, 1923; died in the Duke Hospital Feb. 19, aged 60.

Van Urk, Jules Blan Ⓜ Carthage, Mo.; Columbia University College of Physicians and Surgeons, New York City, 1931; on the staff of the McCune-Brooks Hospital; died Feb. 13, aged 56.

Van Vranken, Gilbert, South Pasadena, Calif.; University of the City of New York Medical Department, New York City, 1892; formerly practiced in Passaic, N. J., where he was on the staffs of the Passaic General Hospital and St. Mary's Hospital; died Dec. 30, aged 93, of arteriosclerotic heart disease.

Walker, Nora May, Champaign, Ill.; University of Michigan Homeopathic Medical School, Ann Arbor, 1893; died Jan. 12, aged 98.

Watkins, Emory Clifford, Brooklet, Ga.; University of Louisville (Ky.) Medical Department, 1907; died in Asheville, N. C., Feb. 14, aged 78.

Weinmann, Max Hamilton Ⓜ Orange, N. J.; University and Bellevue Hospital Medical College, New York City, 1910; at one time practiced in Newark, where he served as a physician to the public school system; for many years medical examiner for the Metropolitan Life Insurance Company; associated with St. Mary's Hospital; died in the Beth Israel Hospital in Newark Feb. 15, aged 72.

Welch, John Orr, Van Nuys, Calif.; Starling-Ohio Medical College, Columbus, 1912; for many years practiced in Columbus, Ohio; died Feb. 11, aged 79.

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Westhofen, Rudolph Charles Ⓜ Milwaukee, Wis., Milwaukee Medical College, 1902; veteran of World War I; served on the staff of St. Luke's Hospital, where he died Feb. 8, aged 81.

White, John Blackshear Jr. Ⓜ Montgomery, Ala.; Tulane University School of Medicine, New Orleans, 1946; served a residency at St. Joseph's Infirmary in Atlanta and the Veterans Administration Hospital in Chamblee, Ga.; specialist certified by the American Board of Surgery; veteran of World War II; associated with Jackson Hospital and Clinic, Professional Center Hospital, and St. Jude's Catholic Hospital; died in Atlanta Feb. 13, aged 37.

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Woodruff, Robert Henry, Springfield, Ill.; Northwestern University Medical School, Chicago, 1904; veteran of World War I; chief of vital statistics of the Illinois Department of Public Health; died in St. John's Hospital Feb. 14, aged 83.

Wright, Laforest Julian Ⓜ Corinne, Maine; University of Vermont College of Medicine, Burlington, 1905; past-president of the Penobscot County Medical Association; past-president of the Bangor Lions Club; died Feb. 9, aged 78.

Young, Mason Pressly Ⓜ Anderson, S. C.; Jefferson Medical College of Philadelphia, 1913; fellow of the American College of Physicians; for many years a medical missionary in China; died in the Anderson Memorial Hospital Feb. 6, aged 72.

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clinic in 1936; a group of industrial and academic leaders in 1943 formed the Spies Committee for Clinical Research to provide financial support for his projects; famed for his part in wiping out pellagra in the southern states and tropical anemias from Cuba and Puerto Rico; applied nicotinic acid as a treatment for pellagra, which reduced the mortality rate from the diseases from 54% to nothing; was the first to use thiamin and synthetic folic acid in the treatment of anemic diseases; since 1943 member of the food and nutrition board, National Research Council; from 1941 to 1947 a consultant to the Secretary of War on tropical medicine; in 1938 was American delegate to the United International Congress of Tropical Medicine in Amsterdam and the following year to the third International Neurological Conference in Copenhagen; past-president of the Interstate Postgraduate Medical Association of North America; at one time councilor of the Harvard Medical Alumni Association; received the Distinguished Service Award of the American Medical Association in 1957; recipient of the Research Medal of the Southern Medical Association and the Orden de Carlos Manuel de Cespedes decoration, highest award of the Cuban government; awarded the rank of Comendador (Exalted Knight), Order of Honor and Merit, Cuban Red Cross; the Academy of Science in Havana, Cuba, presented him the Carlos J. Finlay Medal with the rank of Comendador, Dec. 3, 1954; the Senate and House of Representatives of the Commonwealth of Puerto Rico passed a joint resolution citing his work for the people and hospitals of that island; on July 22, 1957, House Concurrent Resolution, No. 216, was introduced by Hon. Sam Rayburn, Speaker of the U. S. House of Representatives: "Resolved by the House of Representatives (the Senate concurring), that the Congress and the American people hereby express their gratitude to Dr. Tom D. Spies for his noteworthy medical achievements towards alleviating the sufferings of his fellow men and for his outstanding contributions to the knowledge of the science of human nutrition especially in the field of earlier and better methods of diagnosis and treatment of nutritional deficiency diseases"; given the John Phillips Memorial Award by the American College of Physicians in 1939 and the same year was the first person to receive a citation from the Medical Association of Alabama; other awards include the Award of Distinction of the American Pharmaceutical Manufacturers Association, the Oscar B. Hunter Memorial Award of the American Therapeutic Society, and the Charles V. Chapin Memorial Award by the City of Providence (R. I.); received scrolls of honor from the Jefferson County Medical Association and the City Commission of Birmingham; in 1939, *Time* magazine named him "one of the men of the year, outstanding in comprehensive science"; received a certificate of appreciation from the War Department in 1947 for his lectures on nutritional deficiencies to the classes at Army Medical School; on Jan. 27, 1953, the title of Professor Honoris Causa de la Facultad de Medicina de la Universidad de la Habana was conferred by the University of Havana; was guest editor for the March, 1955, *Postgraduate Medicine*, a special issue devoted to studies in nutrition and metabolism by him and his associates; delivered the first Dickinson Lecture at the Chicago Academy of Sciences in 1952, and the 46th Mary Scott Newbold Lecture of the College of Physicians of Philadelphia; on June 12, 1944, the honorary degree of doctor of science was conferred on him by the University of the South, Sewanee, Tenn.; author or co-author of a number of books and sections of books; died of multiple myeloma in the Memorial Center for Cancer and Allied Diseases, New York City, Feb. 28, aged 57.

Stark, Walter W., Midwest City, Okla.; St. Louis College of Physicians and Surgeons, 1919; died Jan. 20, aged 70.

Sternfels, Arthur Francis, St. Louis; St. Louis University School of Medicine, 1910; died Feb. 18, aged 73.

Sutherland, Robert Thomas Ⓜ Oakland, Calif.; University of California School of Medicine, San Francisco, 1908; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; past-president of the Alameda County Medical Society; on the staff of the Highland–Alameda County Hospital; died Feb. 17, aged 76.

Thorne, James I. Ⓜ Miami, Fla.; Creighton University School of Medicine, Omaha, 1906; for many years practiced in the Philippines and served in the U. S. Army Intelligence Service; died Feb. 23, aged 79.

Titus, Jerome Hill Ⓜ Ontario, Calif.; Rush Medical College, Chicago, 1900; member of the American Academy of General Practice; veteran of World War I; past-president of the Ontario Rotary Club; member of the staff of the San Antonio Community Hospital in Upland, where he died Feb. 8, aged 83.

Toops, Cresswell Seth, Columbus, Ohio; Ohio State University College of Medicine, Columbus, 1915; for many years physician for the Industrial Commission for the state of Ohio; died in the Mount Carmel Hospital Feb. 15, aged 70.

Turtz, Charles Aaron Ⓜ New York City; New York Homeopathic Medical College and Flower Hospital in New York City, 1915; specialist certified by the American Board of Ophthalmology; member

Cornwall (N. Y.) Hospital and the New York City Hospital; died in the Veterans Administration Hospital Feb. 27, aged 81.

Muncy, Paul Everette Ⓜ Covington, Ky.; Eclectic Medical College, Cincinnati, 1938; member of the American Academy of General Practice; vice-chairman of the board of trustees of Union College in Barbourville; associated with St. Elizabeth Hospital and William Booth Memorial Hospital, where he died Feb. 15, aged 58.

Nixon, Isabelle Beaty, Mount Vernon, Ohio; Cleveland Homeopathic Medical College, 1899; died Feb. 19, aged 86.

Purdy, Calvin S. Ⓜ Buckley, Mich.; Saginaw (Mich.) Valley Medical College, 1902; also a druggist; for many years county coroner; died in the Munson Hospital, Traverse City, Feb. 19, aged 81.

Raia, Paul J. Ⓜ Brooklyn; New York Homeopathic Medical College and Flower Hospital, New York City, 1921; fellow of the American College of Surgeons; on the staff of St. Mary's Hospital; died in Long Beach Feb. 3, aged 62, of acute myocardial infarction.

Randel, William Adonijah Ⓜ Fort Pierce, Fla.; University and Bellevue Hospital Medical College, New York City, 1899; specialist certified by the American Board of Otolaryngology; fellow of the American College of Surgeons; formerly associated with the Manhattan Eye, Ear and Throat Hospital and New York Post-Graduate Medical School in New York City; at one time practiced in Mount Vernon, N. Y., serving as treasurer of the Mount Vernon Medical Society, and on the staff of the Mount Vernon Hospital; died Feb. 13, aged 82.

Rehn, Adolph Theodore Ⓜ Lapeer, Mich.; Detroit College of Medicine and Surgery, 1934; interned at the City of Detroit Receiving Hospital; specialist certified by the American Board of Psychiatry and Neurology; member of the American Psychiatric Association; medical superintendent of the Lapeer State Home and Training School; died in the Lapeer County General Hospital Feb. 10, aged 52, of ruptured dissecting aortic aneurysm.

Riney, Fred Harold Ⓜ Mingo Junction, Ohio; University of Kansas School of Medicine, Kansas City, Kan., 1908; for many years member and president of the board of education; served as president of the Mingo National Bank; on the staffs of the Gill Memorial Hospital and the Ohio Valley Hospital in Steubenville, where he died Feb. 22, aged 74.

Searles, Karl Fader Ⓜ Flint, Mich.; University of Vermont College of Medicine, Burlington, 1934; interned at the Waterbury (Conn.) Hospital; served a residency at the Woman's Hospital and Children's Hospital in Detroit; member of the American Academy of General Practice; died in the McLaren General Hospital Feb. 21, aged 50.

Segal, Robert Ⓜ Venice, Calif.; Tulane University School of Medicine, New Orleans, 1933; veteran of World War II; died in February, aged 49.

Shaffer, Louis Ⓜ New York City; Fordham University School of Medicine, New York City, 1918; died Dec. 28, aged 71, of occlusive coronary arteriosclerosis.

Smith, Warren A., Berrien Springs, Mich.; the Hahnemann Medical College and Hospital, Chicago, 1903; for many years health officer; past-president of the Berrien Springs Lions Club; on the staff of the Mercy Hospital in Benton Harbor; died in Orlando, Fla., Feb. 17, aged 83.

Snyder, Jacob Daniel, Washington, Pa.; University of Pennsylvania Department of Medicine, Philadelphia, 1903; for many years practiced in Boston; died Feb. 13, aged 83.

Spies, Tom Douglas Ⓜ Birmingham, Ala.; born in Ravenna, Texas, Sept. 21, 1902; Harvard Medical School, Boston, 1928; interned at the Peter Bent Brigham Hospital, Boston, and the Lakeside Hospital, Cleveland; specialist certified by the American Board of Internal Medicine; fellow of the Royal Society of Tropical Medicine and Hygiene (England); member of the American Academy of General Practice, International Society of Hematology, International Society of Internal Medicine, Phi Beta Kappa, Sigma Xi, Society for Experimental Biology and Medicine, Southern Medical Association, Central Society for Clinical Research, American College of Physicians, Association of American Physicians, American Association of Pathologists and Bacteriologists, American Association for the Advancement of Science, American Association for Cancer Research, American Institute of Nutrition, American Public Health Association, American Society of Parasitologists, American Society of Tropical Medicine, American Society for Clinical Investigation, American Society for Experimental Pathology, American Society for Pharmacology and Experimental Therapeutics, American Therapeutic Society, and others; honorary member of Sociedad Cubana de Salubridad Pública and the Puerto Rico Medical Association; a teaching fellow and later instructor at the Western Reserve University, Cleveland, 1931-1935; assistant and associate professor of medicine, University of Cincinnati, 1935-1947; joined Northwestern University Medical School, Chicago, as professor and chairman of its new department of nutrition and metabolism in 1947, with headquarters in Chicago and with clinical work done at the Hillman Hospital in Birmingham, where he became director of the nutrition

Horner, Earl Hartle, St. Petersburg, Fla.; Jefferson Medical College of Philadelphia, 1902; died in St. Anthony's Hospital Feb. 22, aged 81.

Hubbard, James Edward Ⓜ Baltimore; University of Maryland School of Medicine, Baltimore, 1912; formerly practiced in Huntington, W. Va., and was vice-president of the Cabell County Medical Society; during World War I served overseas with the American Expeditionary Force; died Feb. 23, aged 70.

Hunter, Robert Marvin, Clinton, Ark.; University of Arkansas School of Medicine, Little Rock, 1911; died Feb. 20, aged 81.

Jones, Charles David Ⓜ Malden, Mass.; Harvard Medical School, Boston, 1889; specialist certified by the American Board of Ophthalmology; died Feb. 16, aged 96.

Kelling, George A. Ⓜ Waverly, Mo.; St. Louis College of Physicians and Surgeons, 1903; a director and member of the staff at the Kelling Clinic; served as a courtesy staff member of the Lexington (Mo.) Memorial Hospital and the John Fitzgibbons Memorial Hospital in Marshall; died Feb. 24, aged 78.

Kercheval, Clarence K., Ashland, Ky.; University of Louisville Medical Department, 1908; past-president of the Boyd County Medical Society; died Feb. 13, aged 87.

Less, Ernest, Cheektowaga, N. Y.; Universität Rostock Medizinische Fakultät, Rostock, Mecklenberg, Germany, 1920; formerly a resident at the Huntington (W. Va.) Memorial Hospital; served as honorary staff member at St. Francis Hospital in Buffalo; died Feb. 17, aged 65.

Lewis, Silas Arthur Ⓜ North Hollywood, Calif.; Long Island College Hospital, Brooklyn, 1910; fellow of the American College of Surgeons; associated with the Presbyterian Hospital-Olmsted Memorial Los Angeles; died in San Gabriel Feb. 18, aged 83.

Link, Marshall Edwin, Goodlettsville, Tenn.; Vanderbilt University School of Medicine, Nashville, 1892; served as a member of the state legislature; president of the White's Creek Bank & Trust Company; died Feb. 17, aged 91.

McCubbin, James Burlie, New York City; Washington University School of Medicine, St. Louis, 1907; formerly practiced in Fulton, Mo.; died Feb 12, aged 75.

McCurdy, Gordon Judson Ⓜ Phoenix, Ariz.; University of Michigan Medical School, Ann Arbor, 1927; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology, American Laryngological, Rhinological and Otological Society, American Society of Ophthalmologic and Otolaryngologic Allergy, and the American College of Allergists; associated with St. Joseph's Hospital and the Good Samaritan Hospital, where he died Feb. 14, aged 57.

McDonald, Charles Sidney, Jonesboro, La.; University of Arkansas School of Medicine, Little Rock, 1905; served as parish coroner; received a citation from President Franklin D. Roosevelt for meritorious service while a member of the Jackson Parish Selective Service Board; died Feb. 13, aged 82.

McEvoy, Arthur Francis Jr., Ogdensburg, N. Y.; Long Island College of Medicine, Brooklyn, 1949; interned at the Ellis Hospital in Schenectady, where he served a residency; certified by the National Board of Medical Examiners; from August, 1954, to August, 1956, an officer in the medical corps of the U. S. Navy Reserve; on the staff of St. Lawrence State Hospital; where he died Feb. 14, aged 35.

McMurray, John Boyd ⓂWashington, Pa.; born in Independence Oct. 23, 1878; College of Physicians and Surgeons, Baltimore, 1901; specialist certified by the American Board of Ophthalmology and the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology, of which he served as vice-president in 1935, and the American Laryngological, Rhinological and Otological Society; Vice-Chairman, Section on Laryngology, Otology and Rhinology of the American Medical Association, 1934-1935; veteran of World War I; served as director and since January, 1936, president of the Washington Union Trust Company, until it merged with Peoples First National Bank; associated with the Washington Hospital, where he died Feb. 18, aged 81.

Masten, Charles Howard Ⓜ Thompson, Conn.; McGill University Faculty of Medicine, Montreal, Que., Canada, 1893; at one time practiced in Worcester, Mass.; died Feb. 20, aged 91.

Meredith, Evert Waitman Ⓜ Port Huron, Mich.; Johns Hopkins University School of Medicine, Baltimore, 1923; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; certified by the National Board of Medical Examiners; past-president of St. Clair County Medical Society; associated with the Mercy Hospital and the Port Huron Hospital; died Feb. 15, aged 61.

Moretti, Raffaele, Santa Cruz, Calif.; Universita degli Studi di Firenze Facolta di Medicina e Chirurgia, Italy, 1904; died Feb. 21, aged 83.

Morrow, Albert Sidney Ⓜ New York City; University and Bellevue Hospital Medical College, New York City, 1901; fellow of the American College of Surgeons; veteran of World War I; consultant, of the Association for Research in Ophthalmology; fellow of the American College of Surgeons; veteran of World War I; served on the faculty of his alma mater; consultant, Prospect Heights Hospital, Brooklyn; associated with the Bird S. Coler Memorial Hospital and Home, Metropolitan Hospital, and Flower and Fifth Avenue Hospitals; died in the Columbia–Presbyterian Medical Center Feb. 12, aged 68.

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Turtz, Charles Aaron Ⓐ New York City; New York Homeopathic Medical College and Flower Hospital in New York City, 1915; specialist certified by the American Board of Ophthalmology; member

Relapses occurred most often in the lower thoracic and the lumbar vertebrae. Involvement of the hip and knee joints was much less frequent. The time required to establish the diagnosis was up to six months in 42.8%, up to one year in 20.9%, up to two years in 15.6%, up to three years in 5%, and four or more years in 3.5%. Tuberculostatic drugs were withheld until the diagnosis was established. Treatment, preferably in a sanatorium, usually required two to three years. Adequate immobilization and rest of the affected area were necessary. Chemotherapeutic treatment did not shorten the duration of the rest cures. In patients who were getting tuberculostatic treatment vertebrotomy was recommended for vertebral foci. The results with laminectomy were not as good, and this procedure was abandoned.

Transverse paralysis has become a more frequent complication of tuberculosis than meningitis. If it is not controlled within a year, the patient remains crippled for life. Failures were much less frequent with three years of sanatorium treatment than with short-term treatment. Chemotherapy reduced the tendency to relapse from 19.9 to 9.1% and the death rate from 9.7 to 3.8%. Resections in tuberculous joint diseases frequently gave satisfactory functional results. Postoperative function was particularly good after synovectomy in patients with tuberculous knee joints. Much of the disability associated with this disease could be prevented by an early diagnosis and adequate treatment.

After-Effects of Irradiation or Operation for Uterine Carcinoma.—Böckler and Prinz of Frankfurt (*Geburtsh. u. Frauenh.* [no. 10] 19:858-867, 1959) reported on the changes in the upper urinary passages in 157 patients who had carcinoma of the uterine cervix and who were treated by irradiation or operation. Seven patients in whom the uterine carcinoma was cured died of another form of cancer, but none of these patients had changes of the urinary passages. Of the other 150 patients, 51 died of uremia and 106 had congestions in the upper urinary passages due to mechanical causes. Of these 64 had hydronephrosis. Other changes were due to secondary infections with or without parenchymal involvement. Excretory disorders more frequently affected the right side than the left. Of the patients with bilateral hydronephrosis 67% died of uremia. Hydronephrosis and pyonephrosis were twice as frequent in patients treated only by irradiation than in those operated on and receiving postoperative irradiation.

Of 48 ureteric compressions 33 occurred in the immediate vicinity of the bladder and in most cases the only cause was the scar tissue. About 65% of the hydronephrotic changes were asymptomatic and many of them remained undetected clinically. Of 29 patients in whom a relapse-free cure of the carcinoma was achieved 16 had severe hydronephrosis and pyonephrosis. Of the women with urinary congestion 15.4% were free from cancer at autopsy. Five of them died of uremia. All had been given postoperative irradiation to prevent a relapse. Autopsy revealed in all changes in the pelvis minor due to scar tissue. Systematic urologic follow-up examinations are, therefore, very important.

Biguanide for Diabetes.—G. Seydl and H. Schulleri of Kassel (*Med. Klin.* 54:1081-1082, 1959) treated 15 adolescent and 30 older diabetic patients with tablets containing 50 mg. of phenylethylbiguanide and 200 mg. of paraoxypropiophenone. They gave three tablets daily. Severe intolerance necessitated discontinuance of the treatment in nine patients; seven patients tolerated the preparation after treatment had been interrupted for a short time. Simultaneous administration of digestive enzymes or antihistaminics did not influence the toxicity. In young diabetics whose blood sugar level was 300 mg. or more, either the insulin dose was reduced to two-thirds or the patients' metabolic condition was satisfactorily controlled. This appeared to be the main indication for treatment with the biguanide.

INDIA

Histidine Estimation and Pregnancy.—S. J. Joglekar and co-workers (*J. Obst. & Gynec. India,* vol. 10, December, 1959) found repeated estimations of histidine excretion in urine valuable in assessing the prognosis in patients with threatened abortion. The method is easier than examination of vaginal smears. Histidine may be excreted by normal nonpregnant women but in a smaller quantity. With calorimetric procedures, negative results are obtained in 88% and positive results in 12% of nonpregnant women and positive results in 86% and negative in 14% of pregnant women. The figure for nonpregnant women varied from 56 to 120 mg. and for pregnant women from 120 to 628 mg.

Both qualitative and quantitative tests made on the same patients indicated that the qualitative test was not reliable for a diagnosis of pregnancy. A series of 146 women were studied clinically and cytologically, and 24-hour specimens of urine were examined to determine the prognosis in patients with threatened abortion; 23 patients were found to be normal and nonpregnant. In these the 24-hour excretion of histidine varied from 56 to 120 mg; 48 women with normal pregnancy in various trimesters excreted between 120 and 620 mg. Of these four were examined throughout pregnancy and in all the histidine excretion increased steadily till the ninth month. After delivery it returned to the normal prepregnancy level. There were 59 patients with threatened abortion. Two of these continued with pregnancy and the rest aborted. Their histidine excretion varied from 62.5 to 518.0 mg.

Of those with high histidine excretion three were examined when the histidine level was found to drop and all of them aborted within a month. Thus

FOREIGN LETTERS

BRAZIL

Gastrointestinal Trypanosomiasis.—Dr. J. M. de Rezende (*Rev. Goiana de Medicina* 5:193, 1959) called attention to the gastrointestinal form of Brazilian trypanosomiasis. The subjective complaints that help one in making a correct diagnosis include dysphagia, pain on swallowing, regurgitation, epigastric pain, hiccup, dispepsia, meteorism, and constipation. Enlargement of parotid glands, esophageal dysrhythmia, morphologic or dynamic changes in the stomach and duodenum, and gaseous distention of the splenic flexure of the colon are the chief objective findings. Megaesophagus and megacolon are the end result of the associated motor disturbances. In 52% of the patients with megaesophagus, epigastric or retrosternal pain that had no relationship to the intake of solid food but which was immediately relieved by the ingestion of fluids was noted. This symptom was thought to result from a spasm in the lower third of the esophagus or from an esophagitis due to food stasis in that area.

GERMANY

Meconium Plug Syndrome.—E. Willich (*Arch. Kinderh.* 159:276, 1959) reported that although the meconium plug syndrome is not rare it is not widely known. Its main symptoms are similar to those of intestinal obstruction, for which it is easily mistaken. Symptoms occur shortly after birth, mostly in premature infants. Roentgenographic findings vary according to the duration of the occlusion and the location of the plug. There may be marked delay in emptying of the stomach and passage of meal through the intestines with distinct variations in tone and evidence of dilatation of the small intestine, distension of the colon, and absence of air in the distal colon. The location of the occlusion can sometimes be detected by the change in caliber of the intestine.

In the differential diagnosis organic stenoses or atresia must be considered. In the adrenogenital salt-loss syndrome there is an absence of visible gastric peristalsis. The symptoms of meconium ileus sometimes resemble those of the meconium plug syndrome. Barium enema is a valuable diagnostic aid. Meconium inspissation due to lack of postnatal trypsin activity and relative disturbances of intestinal peristalsis give rise to the meconium plug syndrome. In mild cases, the relatively benign form of occlusion may be overcome by merely inserting a thermometer or a finger. Sometimes the meconium is discharged after a barium meal. When these measures fail, rectal filling with one part of a 3% hydrogen peroxide solution to three parts of a normal saline solution is generally successful.

Pregnancy Reaction of the Neonate.—B. Leiber (*Monatschr. Kinderh.* 107:105, 1959) defined pregnancy reactions of the neonate as the untimely and apparently unsuitable changes occurring in infants of either sex which are due to the effects of placentogenic pregnancy hormones. Clinical manifestations of these changes are proliferation of the mammary gland, secretion of a milky fluid from the infant breast, generalized epithelial proliferation with postpartal desquamation, hypersecretion of sebaceous glands, and vaginal bleeding in newborn girls. In addition there are such internal changes as increased growth of all portions of the internal genitals and transformation and hyperplasia of endocrine glands with increases of endocrine and metabolic functions.

At least five groups of substances are now distinguished among the so-called pregnancy hormones of the placenta. These are choriogenic gonadotropin, estrogen complex, pregnandiol complex (progesterone), ACTH, and the androgens. The most profound changes are caused by the estrogen complex. In addition to the main effects (growth of uterus, pelvis, and skeleton; proliferation of mammary glands, epithelium, and sebaceous glands) there are important side-effects (improvement of oxygen utilization, reduction of sensitivity to oxygen deficiency, and inhibition of hyaluronidase). These reactions of the neonate are essential for the growth, development, differentiation, and protection of the infant's life.

Skeletal Tuberculosis.—Höpfner (*München. med. Wchnschr.* 48:2242, 1959) stated that relapses of skeletal tuberculosis have increased in frequency. Of patients with this disease 89% had in their history either pleurisy or roentgenographic evidence of an earlier pleurisy; 21% had had pulmonary tuberculosis which had been controlled. Roentgenographic evidence of skeletal tuberculosis is obtained in some patients months or years later. A series of 3,230 serologic tests gave widely varying results. Tissue examinations showed positive results in 72%. Roentgenographic examination and tomography were important diagnostic aids. Tomography revealed small osseous foci relatively early.

The items in these letters are contributed by regular correspondents in the various foreign countries.

was obtained in 16, temporary relief (minimum of one year) in 15, and failure in 41. Immediate failures were due to intermittent claudication elsewhere in the same or opposite leg. These constituted about half of the failures. The rest were divided almost equally between early union of the divided tendon without lengthening, onset of ischemic changes leading to amputation, and osteoarthritis. The authors believed that the high failure rate could have been greatly reduced by better selection. They believed that 34 of the 41 patients should not have had this operation.

Penicillin Derivatives.—The *British Medical Journal* (1:559, 1960) criticized the manufacturers of a new penicillin derivative, the potassium salt of 6-(alphaphenoxypropionamido) penicillanic acid (penicillin B) for introducing it before any publications on its properties appeared. Some of the claims made for it have now been substantiated by Garrod (*Brit. M. J.* 1:527, 1960) who compared its antibacterial activity with that of penicillin V and penicillin G. Marked differences in antibacterial activity in vitro were observed in the three preparations. There were greater differences between the activities of penicillins G and V than had been generally recognized. Thus when assayed against certain strains of resistant staphylococci, penicillin V was several times more active than penicillin G. The existence of such differences raised the question whether sensitivity tests performed as a guide to treatment can continue to be carried out solely with penicillin G as is done at present.

The most active derivative against penicillin-resistant staphylococci was penicillin B, next penicillin G, and then penicillin V. Penicillin G was most effective against streptococci, pneumococci, Hemóphilus influenzae, and Proteus strains. Penicillin V and penicillin B were next in order of effectiveness. It would appear that penicillin B is the penicillin derivative of choice for treating resistant staphylococcic infections, and it might be preferred for the treatment of all such infections when facilities for determining resistance are not readily available. Although penicillin B is less active in vitro than penicillin G against streptococci and pneumococci, the higher blood levels achieved with it may compensate for this. Penicillin B was relatively ineffective against the gram-negative species tested.

Assessment of Antithyroid Drugs.—Wayne and coworkers (*Lancet* 1:397, 1960) described a clinical method based on a point system of assessing the results of drugs on thyrotoxicosis. They suggested this as an alternative to repeated estimations of the basal metabolic rate of radioactive iodine studies, which are time consuming and inconvenient for the patient. They allocated points indicating the relative diagnostic value of the various symptoms and signs of thyrotoxicosis. From this they derived a score called the diagnostic index, which was shown to have the same degree of accuracy as estimations of the basal metabolic rate or the results of radioactive iodine estimation.

Dyspnea and effort, increased appetite, finger tremor, and moist hands were given a score of 1; palpitations, tiredness, nervousness, and hot hands were allocated 2 points; excessive sweating and a resting pulse rate of more than 85 per minute received 3 points; a decrease in weight and hyperkinetic movements were given 4 points; and preference for a cold environment, 5 points. If increase of appetite and loss of weight were present together they were rated at 3 and 6 points respectively. Further weighing was allowed in proportion to the actual loss of weight. Remission of the disease was considered to have occurred if the total score or therapeutic index reached and remained within the 0 to 5 range for three successive weeks. When the patient was euthyroid, he or she was given a maintenance dose of the drug for three months and then treatment was stopped to see if relapse occurred.

This method was capable of statistical analysis, and a dose response curve showed that the therapeutic response to antithyroid drugs was linear with time. There was also absence of any relationship between the initial severity of the condition and the rate of therapeutic response. By use of this method of assessment, the effectiveness of the antithyroid drugs potassium perchlorate, methylthiouracil, and carbimazole was compared. Methylthiouracil in doses of 600 mg. daily for two weeks, followed by 300 mg. daily, was as effective as 1 Gm. of potassium perchlorate daily, but carbimazole was less effective than the others. Potassium perchlorate was considered the drug of choice as, in effective doses, it appeared less likely to produce skin rashes or blood dyscrasias. In large doses, however, it caused skin sensitization and granulocytopenia.

Corticosteroids in Ulcerative Colitis.—Truelove (*Brit. M. J.* 1:464, 1960) compared the effectiveness of systemic to local corticosteroid therapy in the treatment of ulcerative colitis. Although the value of corticosteroids for this purpose is well established there are no published data on the most effective method of administration. The patients selected for the comparison were suffering from ulcerative colitis with radiologic and sigmoidoscopic evidence of active disease. Those whose disease was confined to the rectosigmoid junction and had severe attacks were excluded. Patients were allotted to one of three groups by random selection. One group of 40 patients was given 5 mg. of prednisolone four times a day by mouth, another group of 40 received a nightly rectal drip of hydrocortisone hemisuccinate sodium or prednisolone 21-phosphate, and the third group of 40 had combined oral and local therapy. The effect of treatment was assessed by determining the number of patients in each group who went into rapid clinical remission repeated readings for histidine excretion are necessary. A sudden drop in the level definitely indicates interruption of pregnancy. In 10 patients a diagnosis of missed abortion was made, and the histidine level in these corresponded to those of nonpregnant women. Six women with complete abortion also showed histidine levels comparable to those of nonpregnant women. It was concluded that the critical level of histidine excretion in normal nonpregnant women and pregnant women with live fetuses could be taken as 120 mg. in 24 hours. Lower figures might be obtained in nonpregnant women or pregnant women in whom the fetus is dead or abortion has occurred. With normal pregnancy the figures are higher.

Serum Protein Pattern in Carcinoma.—Goswami and Barua (*Indian J. Med. Sc.*, vol. 14, January, 1960) studied the changes in serum protein in a series of 40 patients with laryngeal carcinoma. Secondary metastases in lymph nodes were present in all the patients, and the tumor belonged to grade 2 in all but two who had grade 3 tumors. The electrophoretic protein pattern was studied before starting any treatment. Five of the patients had received two exposures of 440 volts for 5 and 10 minutes, which were considered insufficient to cause any alteration in the protein pattern. The results showed a slightly lower total serum protein level than in normal patients. The level was not low enough to constitute a definite state of hypoproteinemia. The albumin fraction, however, showed a marked reduction, and this reduction was greater in those with grade 3 than in those with grade 2 tumors. The alpha 1, alpha 2, and gamma globulin levels showed some increase which was most marked with the alpha 2 component, while the gamma globulin was within normal range in some patients. The beta globulin level showed no deviation from normal. Thus the significant changes were reduction in serum albumin and increase in alpha 2 globulin levels.

UNITED KINGDOM

Renal Homografts.—Generally a renal homograft is rejected because of the antibody reaction between the tissues of the graft and those of the donor. This homograft reaction is to some extent delayed by irradiation of the donor or by giving corticosteroids. Calne (*Lancet* 1:417, 1960) has modified the homograft reaction in kidney transplantation in dogs by the administration of the antimetabolite and antimitotic drug 6-mercaptopurine. In donor and recipient dogs of different breeds a kidney was removed from the donor and transplanted to the right iliac fossa of the recipient. The renal vessels of the donor's kidney were anastomosed to the iliac vessels of the recipient and the ureters implanted into the bladder. In another group, bilateral nephrectomy was done at the same time as the renal homotransplantation. A dose of 2.5 to 5.0 mg. per kilogram of body weight of 6-mercaptopurine was given daily, intravenously at first and later orally.

Although many dogs died from oliguria in 10 to 14 days, there was no sign of a homograft reaction in the kidneys. One dog survived 47 days and then died of pneumonia, but the grafted kidney was normal macroscopically and showed no evidence of the homograft reaction. Both animals passed concentrated urine up to the time of their death. Generally renal homografts do not survive after four to eight days, at which time they show massive cellular infiltration. It is evident that 6-mercaptopurine can modify the rejection of a renal homograft that usually occurs. Its use might offer an approach to renal homografting in man, especially in patients with chronic uremia in whom homograft rejection is already depressed.

Physicians' Pay.—In February, the findings of the Royal Commission on Doctors' and Dentists' Remuneration were published in the daily press and the *British Medical Journal* (Feb. 20, 1960). Pay increases for more than 40,000 hospital and family doctors in the National Health Service were recommended by the Commission. For family doctors, an advance of $25 a week on their 1955-1956 average earnings was proposed. Two interim increases since then reduced this amount to $14 a week. The Commission also recommended a special fund of $1,400,000 a year for distinction awards to outstanding general practitioners if the government and the profession can agree on a scheme.

For consultants, distinction awards are to be increased in number and amount. The Commission suggested a new A Plus award of $11,200 a year for 100 highly qualified specialists. There should also be 300 A awards of $8,400; 800 B awards of $4,900; and 1,600 C awards of $2,100. At present the top award is $7,000. Immediate payment of 31 million dollars for family doctors and 25 million dollars for hospital doctors and dentists was proposed. These would cover the years since 1957, when the Commission was appointed. At that time the physicians were angry because their pay claim of 24% had not been met. The increases proposed by the Commission would raise 1955-1956 earnings by about 20%. The Commission has tried to improve the young doctor's lot, whether in hospital or general practice, as, more than anyone else, he has been underpaid.

The Commission proposed a pay review body which would advise the Prime Minister. For general practitioners an average net income of $6,790 after allowing for practice expenses was proposed. The corresponding average in 1955-1956 was $5,530.

Tenotomy of the Tendo Achillis for Intermittent Claudication.—Boyd and Bloor of Manchester (*Brit. M. J.*, Feb. 20, 1960) performed subcutaneous tenotomy of the tendo achillis for the relief of intermittent claudication in 72 patients. Complete relief

CORRESPONDENCE

MISUSE OF SYMPATHY

To the Editor:—The emphatic views of Dr. Sidney Bolter on "The Misuse of Sympathy" (Medicine at Work, *J. A. M. A.* 172:335 [Jan. 23] 1960) appear to be entirely original; I know no other doctor who feels that sympathy has little place in the practice of medicine. Dr. Bolter writes as a psychiatrist, but reading his paper (*J. Michigan M. Soc.* 57:1708, 1958) leaves one with the impression that he has the entire practice of medicine in mind when he writes: "Unfortunately sympathy is not a scientific instrument. It cannot be dispensed in any measurable amount, kill bacteria, remove or alter the function of diseased organs, immunize against ill health, and, above all, it cannot foster psychological growth and maturation. Under the psychiatric microscope, sympathy can only be viewed as being saprophytic, feeding on emotional decay."

Medicine has long been held back in its development by people not inclined to put their theories and practices to test in a way generally accepted in other sciences. It is ironic that now it should be hospitable to pseudoscientism, an undue regard for the mere forms, manners, and jargon of science. The approach of organized common sense known as the scientific method is as important in medicine as it is in other fields. We are living in the happy era when this fact is being increasingly recognized. If a scientist is a person who bases his opinions on evidence, more and more doctors are beginning to act like scientists. Progress in the basic sciences is now accepted as an essential condition of advance in the healing arts, and at the bedside standards of intellectual excellence in observing, deducing, and reporting show a gratifyingly steady improvement. The best of medical work in our time compares favorably in its successful pursuit of truth with the best in other fields. We do not have enough truth yet, but we are getting more and more.

It is, however, one thing to seek understanding, and another to belittle or reject that which one does not understand. Sympathy is not a "scientific instrument;" neither is the blue of the sky or the green of fresh grass. Sympathy cannot be dispensed in measured amounts; neither can the pleasure of duty well done, freedom from pressure, freedom from need, the feeling of being needed, or the hope of an acceptable tomorrow. Yet these nonmeasurable factors are immeasurably important, perhaps essential, to the total health of modern man.

Sympathy can be misused; so can sunshine, mother's milk, or sleep. A few patients may need to be told that they must begin to grow up and that their problems are created, not helped, by the constant presence of a brother on whom they can lean; for such patients showing undue sympathy may merely continue the morbid pattern and stand in the way of the healing process. But the rest of our patients, without exception, are in need of reassurance. The many who are not ill need nothing else; the gravely ill often can be offered little else. Making them feel that they are in competent and watchful hands is as much part of being a doctor as dispensing penicillin in measured amounts.

The doctor has to know his business. Sympathy cannot substitute for science; if it could, mothers and sisters would take our place. But in medicine compassion complements competence; indeed, one can hardly exist without the other. There is no compassion in the incompetent among us, and competence in medicine would be hard to acquire if one did not feel that observing suffering, studying it in detail, and being surrounded by it all the time served the purpose of giving aid. The anguish and agony one sees daily; the blood, sweat, tears, and pus on one's hands; the sights and smells of the sickbed; the grunts and groans and grief; the maimed and the moribund, the broken bones, and the broken lives—all this could not be endured for long were it not for the hope that one can give some help. One does not ordinarily confess this, to others or to oneself; there is no need to do so.

The words of Dr. C. Sidney Burwell, spoken in another context at the opening of the Clinical Meeting of the A. M. A. in Boston in November, 1955, may well end this discussion of science and sympathy in modern medicine: "How fortunate one is to live in this age of medicine! Continuing changes and growth are expected and hoped for. Details will alter; I suspect that the principles of caring for the patient will remain."

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MATERNAL INFLUENZA AND CONGENITAL DEFORMITIES

To the Editor:—Your United Kingdom correspondent reported in The Journal, Feb. 13, 1960, page 729, on the article "Maternal Influenza and Congenital Deformities" (Coffey and Jessop: *Lancet*, p. 935, [Nov. 28] 1959), which describes studies carried out in Dublin, Ireland, during the 1957-1958 epidemic of Asian influenza. From these studies the investigators inferred that women who and showed complete loss of symptoms within two weeks and whose sigmoidoscopic appearances showed a decisive improvement.

About 33% of the patients who took prednisolone only by mouth showed a rapid clinical remission, and 75% of those treated locally showed such remission. There was little to choose between the two corticosteroids used for local treatment, each being more effective than the prednisolone taken orally in the dose used. With combined local and systemic treatment the results depended on the combination used. When prednisolone given by mouth was combined with the prednisolone drip, the results were similar to those of local treatment used alone. When prednisolone by mouth was combined with the hydrocortisone drip, the patients treated showed a rapid remission. Use of this combination was, therefore, considered to be the treatment of choice. It was assumed that the hemisuccinate compound had a local action on the intestinal mucosa and was not absorbed to any extent.

Reduction of Blood Cholesterol Levels.—Heparin is known to lower the blood cholesterol level of animals, but its effect in man is inadequately documented. At best, it has been found to be moderate and erratic. In the hope of finding a more effective and cheaper substance than heparin, which is a sulfated polysaccharide, Constantinides and co-workers (*Brit. M. J.* 1:535, 1960) examined a number of sulfated polysaccharides derived from seaweed. Those with a mannuronic acid unit appeared to be the most promising. They had a greater antilipemic and cholesterol-lowering activity than heparin without any toxic side-effects. They were also able to arrest the progress of preestablished atherosclerosis in rabbits. One of the sulfated polymannuronides, Paritol, was selected for clinical use.

Paritol was given once or twice daily, intravenously or intramuscularly, to 15 hospitalized patients with hyperlipemia and hypercholesterolemia. They were on a constant fat and caloric intake and were studied during a control period before treatment. Total lipid, cholesterol, and phospholipid levels and turbidity values were determined every morning just after rising. Given either intravenously or intramuscularly, Paritol produced a rapid and intense action on elevated serum lipid levels. It caused a return to normal total lipid levels within 24 hours, and normal cholesterol value within 72 hours in most of the patients. The remainder had greatly reduced blood cholesterol levels. The only refractory patient was getting glucocorticosteroid therapy. The antilipemic action was sustained while the Paritol was being given and was gradually reversed after its withdrawal. The minimum effective dose was 2.5 mg. per kilogram of body weight a day. On this dosage Paritol had no anticoagulant action or side-effects and showed a far greater activity than equivalent amounts of heparin. It successfully cleared the serum turbidity of some patients with coronary disease when heparin had failed to do so.

It is anticipated that low subanticoagulant doses of Paritol might permit effective long-term control of hypercholesterolemia without any undesirable effects. Long-acting preparations requiring only one or two intramuscular injections a week would seem to be the ideal method of administration for long-term treatment.

Muscle Relaxants for Tetanus.—The use of muscle relaxants and total paralysis in the treatment of tetanus has never been satisfactorily evaluated because not enough patients have been treated by any one group to justify a statistical analysis. The severity of the infection varies greatly, and many patients may recover without any specific treatment other than taking antitoxin. Alhady and co-workers (*Brit. M. J.* 1:540, 1960) treated 40 patients who had tetanus of varying severity in Malaya, where the condition is comparatively common. All patients received 50,000 to 100,000 units of antitoxin, chlorpromazine, penicillin intramuscularly, and thiopental intravenously. The wound of origin was excised when possible.

If this conservative treatment seemed to be failing, tracheotomy was performed and the patient was totally paralyzed by an intravenous injection of atropine and thiopental followed by administration of succinylcholine chloride. Paralysis was maintained by giving d-tubocurarine chloride intramuscularly with hyaluronidase in a dosage of 4 to 30 mg. every one or two hours. The patients were treated in a respirator and never left unattended. Intermittent positive-pressure respiration was maintained with a respirator through a cuffed endotracheal tube inserted into the tracheotomy opening. Respiratory pressure was adjusted to provide the desired minute-volume. The patients were frequently turned, mucus was sucked out, and the back was heavily percussed to promote the drainage of bronchial mucus and secretions. Of the 40 patients treated, 30 who had mild cases recovered on the routine treatment. The remaining 10 were classified as having severe cases and received the treatment involving total paralysis and assisted respiration. Only two survived.

It was therefore concluded that this form of treatment is of limited effectiveness. Life is prolonged in these cases and the patient ultimately dies not from the direct or indirect effects of the hypertonus and spasms but most probably from the delayed effect of the tetanus toxin on the myocardium. It would seem that survival or death largely depends on the severity of the infection and the amount of circulating toxin rather than on specific treatment other than the administration of antitoxin.

publication of the report in question, and it can now be obtained from the usual outlets of WHO publications. I take the liberty of remarking that someone was a bit lax in allowing the gist of a report of a committee of WHO, whose headquarters are in Geneva, to appear as news from India and in freely using the supposedly banned and certainly undesirable word "leper."

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DETECTION OF HEPATITIS CARRIERS

To the Editor:—Bang and associates (*J. A. M. A.* 171:2303 [Dec. 26] 1959) have analyzed the distribution of 39 cases of homologous serum jaundice among 1,371 recipients of blood transfusions. The authors classify recipients into three groups. Group 1 received no transfusions of blood with an SGO-T level above 40 units; group 2 received one or more transfusions of blood with a level of activity between 41 and 99 units; and group 3 received at least one transfusion of blood with an SGO-T level above 99 units. One would assume that so reasonable a classification could not bias the results of the study. Unfortunately, it does affect the final results. Statistical models have been constructed which embody this classification but in which there is no correlation between SGO-T level and contamination with the hepatitis virus. In each model, the apparent incidence of hepatitis is greater in group 2 than in group 1 and greatest in group 3.

This strange result can be explained. The more transfusions a patient is given, the less likely it becomes that all the transfusions will be made with blood with an SGO-T level under 40 units. Thus, it becomes increasingly less likely that a patient will belong to group 1. At the same time, the patient's chances of getting hepatitis vary directly with the number of transfusions he receives, for each puts him at additional risk. This classification therefore insures that patients who are likely to get hepatitis (multiple transfusions) are less likely to be found in group 1 ("normal" SGO-T levels).

The authors conclude that 9 rather than 39 cases of hepatitis would have been found if only normal SGO-T level blood had been used. These 9 cases developed among the 603 patients in group 1. How many cases would have developed among the 768 other recipients? Simple proportion would seem to suggest 11 more cases, for a total of 20. This number is still too low. If the patients now in groups 2 and 3 had received only blood with an SGO-T level below 41 units, their chances of getting hepatitis would still be higher than in group 1, for they must have received a larger number of transfusions. Bang and others, taking into account the problem of multiple blood transfusions, indicate that the incidence of hepatitis from one blood transfusion with normal SGO-T activity is 0.0058. On this basis it may be estimated that 26 rather than 9 cases of hepatitis would have been found if only blood with a normal SGO-T level had been used.

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To the Editor:—In the article by Bang and others in The Journal, the conclusion is in no way warranted by the evidence, and some readers may be led astray because of erroneous statistical reasoning. Of the total of 1,371 recipients of blood transfusions, a total of 39 developed hepatitis. Of these 39, there were 9 who had received blood with normal SGO-T activity in a group of 603 who received such blood; there were 22 in 624 who had received blood with an SGO-T activity of 41-99 units; and there were 8 in 144 who had received blood with an SGO-T activity above 100 units.

From these data the authors derive results which, they say, are "statistically significant," but no statistically significant conclusions can be drawn from these data. The total number of cases of hepatitis is only 39, far too few to warrant any inferences of importance. These 39 are divided into three cells of 9, 22, and 8 patients, respectively, two of which are too small to be used in any serious statistical calculation, but even if one wishes to use statistics, the conclusion is erroneous. On the hypothesis that SGO-T activity in donor's blood is unrelated to development of hepatitis in recipients, the chi square value is 8.40. With the two degrees of freedom in this case (three cells), it is found that p is about 1/75. In medical literature, "statistically significant" means that p is not more than *1/100*. The authors' conclusion that hepatitis is more likely to develop in recipients of blood with higher SGO-T activity may be correct, but it should not be believed until there is sufficient evidence to warrant it.

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To the Editor:—Since I acted as a statistical adviser to Dr. Bang and his associates for their study on detection of hepatitis carriers by serum glutamic oxalacetic transaminase activity, I have been asked to comment on the letters of Dr. Wiener and Dr. Zeisler criticizing their conclusions.

Dr. Wiener's points are well taken and constitute the reason for the analysis presented in table 4 of the original paper and appearing as the final statement in the summary, in which variations in numbers of transfusions were, in fact, controlled. Unfortunately, there is a gross error in statement 5 of the summary, in which the best estimate of the develop influenza while pregnant, especially during the first trimester, are more likely to give birth to children with congenital deformities. These studies and the above noted inference were featured in *Time*, Dec. 7, 1959, page 82. I communicated with the editor of *Time*, questioning the validity of the Dublin studies; I received a letter in which they conceded that perhaps their statement that Asian influenza was a possible threat to unborn children "was overly conclusive in its implications."

The readers of The Journal should be fully informed on issues which may cause undue alarm among the public. I would like, therefore, to direct attention to a letter which I sent to the *Lancet* and which was published on page 113 in its Jan. 9, 1960, issue. The contents of my letter follow:

> The article "Maternal Influenza and Congenital Deformities" (*Lancet*, 28 November, 1959, page 935) merits further comment, especially in view of two reports on this subject, the findings of which are contradictory to those of the *Lancet* article. In all likelihood, these reports had not as yet been available to Doctors Jessop and Coffey at the time they completed their study.
>
> Wilson and his co-workers as a result of their investigation [1] concluded that "No significant teratogenic effect of Asian influenza was demonstrated. . . ." It is to be noted that the presence or absence of influenza in the patients they studied was confirmed by hemagglutination-inhibition titer determinations.
>
> Walker and McKee [2] have concluded that "there was no apparent alteration in the number of anomalies in the infants of mothers who had Asian influenza during their pregnancy." In this study serological tests for influenza similar to those employed in Wilson's investigation were also carried out.
>
> On the basis of Walker and Wilson's study one might well question the implications of the Dublin study. Moreover, the methodology of selecting patients for inclusion in the study on the basis of self diagnosis is vulnerable to criticism. This is so, not so much (in this instance of a disease with a high attack rate) because those replying in the affirmative may not have had the disease, but, as Walker's study points out, because those replying in the negative may very well have had the disease.
>
> [1] Teratogenic Effects of Asian Influenza: J. A. M. A., 10 Oct., 1959, p. 638.
>
> [2] Asian Influenza in Pregnancy: Obstet. Gynec. April, 1959, p. 394.

Subsequent to the publication of the Dublin study, Dr. E. Clayton-Jones, general editor of *Cerebral Palsy Bulletin*, a publication of the National Spastics Society of Great Britain, in a letter to the *Lancet*, Dec. 12, 1959, page 1086, cited several cases of congenital deformities in infants born of mothers ill with influenza during pregnancy. He also wrote to me pointing out that there "are obvious objections to the figures from Dublin." In addition he stressed the importance, in evaluation of congenital deformities, of careful follow-up examination over a number of years of the children under study "in case they develop some defects that would be overlooked, . . . or perhaps be nonexistent . . . in the neonatal period."

This information is submitted to provide additional details on an issue which is of extreme interest to the public as well as to the medical profession.

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SEGREGATION IN LEPROSY CONTROL

To the Editor:—In the Foreign Letters section of The Journal, Jan. 9, page 186, is an item entitled "Segregation of Lepers." This item is open to objection.

The report of the World Health Organization's Second Expert Committee on Leprosy, which met in Geneva in August, 1959, does not contain the figures which appear in the report referred to. (As a member of that committee, I can speak with some assurance.) Those figures were contributed in a press release issued by the public information division of WHO headquarters shortly after the meeting ended and the committee was dispersed.

That press release immediately resulted in newspaper headlines, at least in England and the United States, to the effect that the committee had recommended abolition of leprosariums, which was simply not true. Furthermore, the statement in the note saying that "the age-old custom of keeping lepers apart from the rest of the community is unnecessary from the medical point of view" is hardly less misleading. The recommendation of the committee, in keeping with resolutions of several international meetings held in recent years, is that leprosy should be treated more or less as tuberculosis is treated, with hospitals for the care of patients with "open" infective cases, for the treatment of patients of patients suffering from the acute "reactional" episodes of leprosy, for the surgical reconstruction of patients with mutilations, and for the training of personnel and other administrative purposes. The problem of the "recalcitrant" patient (to use the terminology of tuberculosis workers) must also be considered.

The statement about the committee's recommendations on the matter of legislation is also likely to be seriously misunderstood. It was recommended that special laws applying solely to leprosy be abolished and that the control of leprosy and of persons with the disease be taken care of by regulations set up under general laws pertaining to the control of communicable diseases as a whole. That would not, by any means, preclude isolation of some patients if it seems necessary under local conditions in the light of present knowledge of the disease.

The reports of all WHO expert committees remain "classified" until passed on by the WHO executive board at its next meeting. In the present case that meant a delay of at least five months in publication. On Jan. 20 the executive board authorized

MEDICAL FILM REVIEWS

Myxomas of the Heart—Diagnosis and Surgical Management: 16 mm., color, sound, showing time 13 minutes. Prepared in 1959 by C. Frederick Kittle, M.D., James E. Crockett, M.D., T. L. Batchelder, M.D., and Don R. Miller, M.D., Kansas City. Procurable on loan from Kansas University Medical Center, Kansas City 12, Kansas, and on purchase ($60.00) from Churchill Wexler Film Productions, 801 N. Seward St., Los Angeles 38.

This film presents the clinical data and operative procedures for two primary tumors of the left auricle. Preceding the clinical presentation, some statistics regarding this subject and historical factors are presented. Colored drawings are effectively used to demonstrate the subject matter and materially clarify the operative procedures. X-ray studies and physiological data in the cases presented bring out diagnostic factors of importance. The first patient was managed under hypothermia, the lesion being approached from the left side. Results of this operation were unsuccessful due to some uncontrollable factors. However, the second patient responded well to therapy and, after the removal of a large myxomatous type of tumor from the left auricle, the results were very successful. The approach in this patient was through the left auricle from the right side of the chest. During the time in which the approach was being made cardiopulmonary bypass arrangement was used. Pathological characteristics of the lesions, both gross and microscopic, are demonstrated. Complete recovery was demonstrated by showing the patient returning to her usual duties as a housewife. The color photography and narration of this film are excellent. Exposure and technical details are very well presented and described. This is an excellent teaching film for both the undergraduate and graduate area in this discipline of surgery.

Hypospadias, Complete Correction: 16 mm., color, sound, showing time 20 minutes. Prepared in 1959 by and procurable on loan from Howard B. Mays, M.D., 3301 N. Charles St., Baltimore 18.

This is an excellent film on one of the techniques of repair of hypospadias. The operation is carried on in two stages. In the first operation the chordee is repaired and a large area of foreskin is freed and pulled around to later be used in the formation of the urethra. The second operation is performed several months later with the formation of a new urethra from the foreskin flap that has been previously prepared. One can very easily understand the whole procedure. The photography is good, and the discussion is excellent. This is an excellent film for surgeons who do this type of plastic surgery and for surgical house officers.

NEW FILM ADDED TO A. M. A. MOTION PICTURE LIBRARY

Cystic Fibrosis: 16 mm., color, sound, showing time 28 minutes. Prepared in 1959 by Henry B. Bruyn, M.D., Jackson T. Crane, M.D. and Howard L. Steinbach, M.D., San Francisco. Procurable on loan (service charge $4) from Motion Picture Library, American Medical Association, 535 N. Dearborn St., Chicago 10.

In this film there is a clear presentation of cystic fibrosis beginning with the discovery of it in 1938 and going through the history of the disease. The familial and recessive hereditary characteristics are discussed. There is also an excellent discussion of symptoms, the incidence of occurrence, and the various forms in which the disease might present itself. A brief case summary is given indicating the multiple diagnoses which may be made before the correct one is given. It is an excellent review of the physicopathology of the disease and the various tests that can be done to prove the presence of cystic fibrosis. A short resume of therapy such as diet, medication, immunization, and emotional problems is given. The photography and sound production are extremely good, and the film is highly recommended for pediatricians, general practitioners, house officers, and medical students.

ANTIBODIES

I was waiting, the other day, in a doctor's anteroom, and picked up one of those books—it was a work on pathology—so thoughtfully left lying in such places; to persuade us, no doubt, to bear the ills we have rather than fly to others capable of being illustrated. I found myself engaged in following the antics of certain bacilli generically described as "Antibodies." . . . Now I do not doubt the creature thus named to be a poisonous little wretch. Those who know him may even agree that no word is too bad for him. But I am not thinking of *him.* I am thinking of *us:* and I say that for our own self-respect, whilst we retain any sense of intellectual pedigree "antibody" is no word to throw even at a bacillus. The man who eats peas with his knife can at least claim a historical throwback to the days when forks had but two prongs and the spoons had been removed with the soup. But "antibody" has no such respectable derivation. It is, in fact, a barbarism, and a mongrel at that. The man who uses it debases the currency of learning.—Quiller-Couch, A., On the Art of Writing, New York, G. P. Putnam's Sons, 1916.

number of hepatitis cases that theoretically would have occurred with the administration of donor blood with a SGO-T activity of 40 units or less would read 26 cases instead of 9 cases. This is based on the analysis in table 4, in which the theoretically expected number of cases is 22, or one-third less than the 33 which actually occurred. Although the error had the effect of making the effect appear greater than it was, it does not alter the expressed conclusion that "the present results warrant further studies to elucidate whether an abnormal SGO-T activity reflects the presence of hepatitis virus in donor bloods in a sufficiently high percentage of cases to advocate the determination of SGO-T activity as a standard screening measure to be used by the blood banks to minimize the occurrence of homologous serum hepatitis."

I cannot agree with Dr. Zeisler's comment that a probability level of 0.01 is necessary for "statistical significance." There are many problems in interpreting statistical data, but if the tests are appropriate to the data these problems are not solved by rejecting findings which fall between the 0.05 and the 0.01 levels of significance.

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METAHEXIMIDE AS A HYPOGLYCEMIC AGENT

To the Editor:—The abstract of the report "Further Experience with Oral Therapy in Diabetes" (*J. A. M. A.* 172:876 [Feb. 20] 1960) merits comment in view of the statement in it that "these findings suggest that metaheximide is a well-tolerated hypoglycemic agent." In a form letter for mailing list distribution in June, 1959, W. F. Wenner, M.D., of the Upjohn Company, stated the following: "On May 10 we terminated all clinical trials [with metaheximide], for evidence then left little reasonable doubt as to the causative relationship between the use of this agent and the occurrence of jaundice associated with hepatic parenchymal necrosis."

A case of severe liver damage that occurred after the administration of metaheximide was recently reported (Mach and others: *New England J. Med.* 261:438 [Aug. 27] 1959, abstracted in J. A. M. A. 171:2366 [Dec. 26] 1959). In this article the authors comment on the fact that carbutamide and metaheximide, the two sulfonylurea hypoglycemic agents that have been associated with severe hepatocellular damage, both contain an amino group on the phenyl ring. They believe that this aminophenyl grouping confers hepatocellular toxicity on the sulfonylurea agents.

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USE OF ICE COLLAR

To the Editor:—The author of the recent article entitled "Use of Ice Collar in Paroxysmal Auricular Tachycardia" (*J. A. M. A.* 172:556 [Feb. 6] 1960) attributed the abrupt cessation of the arrhythmia to a reflex from temperature receptors in the skin of the neck. According to his report, the ice collar was laid transversely, without any pressure, across the neck at the level of the carotid sinuses while the patient was in the supine position.

A number of other mechanisms appear far more applicable in this instance. The effective response was probably due to the cold or the relatively light pressure of the collar itself on the carotid sinus, which is located immediately beneath the ice collar. In some instances, light stroking over the sinus is adequate. A similar effect might have been inadventently produced by head and neck movements. The application of cold may simulate manual compression of the internal carotid artery, which in turn increased the necessary pressure in the sinus, by producing a temporary spasm of this artery. Reflex discharge of the vagus may also occur on stimulation of the gastrointestinal tract with production of nausea and vomiting. Digitalis was prescribed. Although inadequately maintained, its vagal stimulating action could have been temporarily augmented by any of the above stimuli.

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THINGS OF THE SPIRIT

To the Editor:—It seems incredible to contemplate the medical curriculum and find no emphasis on "the eternal verities," or things of the spirit. If health is to be maintained this aspect of man must be maintained, and if the study of it is not included in the education of a medical student he is not aware of or prepared to treat man's aberrations. This neglect is all too apparent in the life of our time, when so many of the daily radio and television broadcasts are given over to recital of the latest crime news.

The lives of those who do not nurture their spiritual well-being revolve in an imperfect circle. They may be physically healthy and mentally well rounded but spiritually warped. Then the whirling speed of modern existence creates agitation that finally disrupts the machine. It may be compared to an automobile which is driven fast with its wheels out of line, which makes the engine knock and the whole machine shimmy.

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The average age of the patients was 44.1 years when the carcinoma of the cervix was diagnosed and 55.8 years when factitial enteritis was diagnosed, which shows an average interval of 11.7 years between the radiation therapy and the onset of the complicating symptoms.

The involved segment of the ileum was resected, and the intestinal continuity was reestablished, in 3 of the 5 patients with recurrent intestinal obstruction. There were dense stricture formation, fibrosis, and hyalinization in the intestinal wall, and changes characteristic of irradiation in the vascular walls. Ulcers of the mucosa were present in the 3 patients. The 2 remaining patients in this group refused the operation because their intestinal episodes were infrequent. The patient with massive hemorrhage underwent 2 operations, the first for derivation of the ileum and the second for its removal. The intestinal segment removed contained a 6-mm.-diameter ulcer. The patient with a malabsorption syndrome underwent an abdominal exploration, with biopsy of the jejunum, colon, pancreas, and liver. The jejunum and the colon presented changes characteristic of factitial enteritis, while no significant changes were found in the liver or the pancreas. Supportive therapy relieved the patient's diarrhea.

The author emphasizes the importance of recognizing factitial enteritis, for it is a benign process which can be cured by surgical resection of the segment involved. Failure to recognize the recurrent bouts of intestinal obstruction or hemorrhage as a complication of irradiation deprives the patient of a specific curative therapy and may lead to the use of additional irradiation, which will intensify the pathological process.

Definitive Treatment of the Post-Thrombotic Syndrome: The Use of Venograms to differentiate and Delineate Surgical Treatment. G. H. Pratt. A. M. A. Arch. Surg. 80:112-118 (Jan.) 1960 [Chicago].

From the many patients operated on for the post-thrombotic syndrome at St. Vincent's Hospital, New York, the author has selected 250 private patients who received all forms of conservative and surgical therapy. Since 47 patients could not be followed, there remain the cases of 203 for analysis. Eighty-three of the 203 patients responded to the simple but important expedient of elevation above the heart level at night and at many intervals during the day, adequate support betweentimes, and warm packs. Insistence on these measures early and for a long enough time often prevented the development of more serious complications. One hundred twenty patients, however, did not respond to this therapy or were seen too late for it to be expected to succeed. Fifty of these had been operated on already. These patients were separated into 3 categories: (1) those with the large, white, tender, heavy leg with causalgia-like symptoms; (2) those with marked varicosities of the superficial venous system; and (3) those with ulcers, dermatitis, etc. All were subject to recurrents bouts of localized phlebitis; some had embolic phenomena.

All patients with the post-thrombotic syndrome at first are treated with conservative measures, consisting of 3 weeks' hospitalization, with elevation, support, warm packs, anticoagulant therapy, and antibiotics. Those with spasm are given test sympathetic nerve blocks. They are then sent home on a similar regimen, including anticoagulants. One-third (as in the series reported) need no further treatment; the other two-thirds are treated surgically. After venograms show that the deep veins are functioning, many of the patients in group 1 can be relieved by the treatment of the spastic factor. If nerve blocks give temporary relief, sympathectomy is done. Extensive sympathectomy removes the causalgia and also probably opens arteriovenous shunts. If there are enlarged veins, these are removed.

The second surgical group are those patients in whom a severe deep venous occlusion has resulted in the development of tremendous superficial veins. Venograms taken of these patients show that the deep veins recanalize and, when completely opened, function nearly as well as they did before. Dividing the femoral or popliteal veins complicates matters and often results in edema, which cannot be relieved by the superficial system. Since the residual pathology is in the superficial and communicating veins, both of which become valvularly incompetent, these are superficially excised, thus removing the site of repeated attacks of superficial clotting, cellulitis, and dermatitis.

The third and largest group that come to operation are those patients with chronic and recurring ulcers. These are caused by venous stasis and arterial varices. No patient is operated on until the inflammation has subsided. Surgery not only removes the ulcer and fascia but also excises pathological veins and arteriovenous shunts. Skin grafting completes the procedure.

Adductor Myotomy and Obturator Neurectomy for the Correction of Adduction Contracture of the Hip in Cerebral Palsy. H. H. Banks and W. T. Green. J. Bone & Joint Surg. 42A:111-126 (Jan.) 1960 [Boston].

The authors report on 89 patients with cerebral palsy, who were treated by orthopedic surgical procedures for correction of adduction contracture of the hip at the Children's Hospital, Boston, between 1940 and 1956. All these patients were seen on an average of 6 years after the operation, and 22 of them were evaluated from 10 to 17 years postoperatively. Adduction contracture is the most common hip deformity in patients with the spastic

MEDICAL LITERATURE ABSTRACTS

SURGERY

The Ruptured Disk Versus the Protruded Disk. F. A. Palazzo. South. M. J. 53:55-62 (Jan.) 1960 [Birmingham, Ala.].

The author feels that careful differentiation of the lesion in patients with the disk syndrome will lead to a better selection of patients to be treated surgically as against those who will be benefited by conservative treatment. The case histories of 100 consecutive patients, personally examined and operated on for disk lesions, have been analyzed with the intent of making a clinical distinction between those with a protruded disk and those with a disk rupture. The disk lesions found at operation in these 100 patients fall into 3 main groups: (1) ruptured disk; (2) ruptured contained disk; (3) protruded disk.

Ruptured disk refers only to an actual extrusion or rupture of a free fragment of nucleus pulposus into the spinal canal. The extrusion may be partial or complete through the opening torn in the annulus fibrosus and the posterior longitudinal ligament. Occasionally the free fragment of disk material migrates beyond the site of rupture. Ruptured contained disk refers to the fragment which has ruptured beyond the disk interspace and the enclosing annulus fibrosus, but is still encapsulated by a thin membrane, the attenuated posterior longitudinal ligament. This mass is usually lumpy or slightly lobulated. Protruded disk refers to the simple bulging of the intervertebral disk within a stretched annulus fibrosus and posterior longitudinal ligament. Among the 100 patients operated on, 42 had a ruptured disk; 34, a ruptured contained disk; and 23, a *protruded* disk. One patient had no disk lesion, but had only a defect of the isthmus.

No one symptom or sign gives a clue in deciding whether a disk is ruptured or protruded. Though the patients having a protruded disk often had less severe symptoms, many showed as severe a clinical picture as did the groups with a ruptured disk. At operation these patients with the severe findin were found to have a protruded disk which, i effect, acted like the ruptured disk mechanicall the dense adhesions and bony ridges flanking th disk protrusion presented as fixed and unyielding mass as the disk which has actually ruptured. Th simple fluctuant disk protrusion without bony ridg or adhesions occurred in only 4 patients, and probably was to be found chiefly in the 214 patient who received only conservative treatment. Undoubtedly, an occasional patient with ruptured dis is not operated on and responds to conservativ treatment, but usually with some neurologica deficit.

Patients in the groups with ruptured disk (free o contained) are likely to present themselves wit the following combination of symptoms and sign 1. There is severe to excruciating pain, usually constant and frequently occurring at night, makin sleep fitful. 2. The pain is aggravated by factor such as walking, sitting, standing too long, bendin lifting, straining, coughing, or sneezing. 3. Little o no benefit results from traction or a lumbosacra belt. 4. Analgesics and heat are usually ineffective 5. The pain is usually too severe to permit work an does not respond to conservative treatment. 6. Motor and sensory symptoms are seen frequently.

The author feels that the fact that the percentag of ruptured and ruptured contained disks was extremely high in this series was due to the insistenc on performing operations only on patients wh had an ineffective response to conservative treatment, and to the other criteria discussed. It is believed that too high an incidence of simple disk protrusions at operation indicates that too many patients are being operated on who would have been adequately relieved with conservative treatment.

Factitial Enteritis: An Unusual Cause of Intestinal Obstruction, Chronic Blood Loss or Malabsorption Syndrome. W. G. Sauer. J. Iowa M. Soc. 50:1-7 (Jan.) 1960 [Des Moines].

Factitial enteritis is an unusual lesion, resulting from irradiation of malignant tumors of the female genitourinary tract. It may appear many years after irradiation. Seven cases of this late complication of x-ray and radium therapy are reported. Five patients had episodes of intermittent, incomplete obstruction of the small intestine, one had severe hemorrhage from the gastrointestinal tract, and one had a severe malabsorption syndrome.

The place of publication of the periodical appears in brackets preceding each abstract.

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help control infections of enteric origin, the need for immediate surgical treatment became less urgent, and it was accepted that it is permissible to wait a few hours, if necessary, to establish more accurately the diagnosis of acute appendicitis.

The author presents a statistical analysis of appendectomies performed at Blount Memorial Hospital, Maryville, Tenn., during the past 9 years. This hospital has a capacity of 210 beds and is the only hospital in an area of about 65,000 population. There has been an average annual increase in population of 3%. The number of hospital admissions, as well as the number of major operations each year, has shown an annual increase of about 5%. For the past 7 years the staff's tissue committee has made annual studies of the primary appendectomies performed. All appendectomies which showed polymorphonuclear infiltrations in the mucosa or muscularis were diagnosed as "acute suppurative appendicitis." All others were placed in the "nonsuppurative appendicitis" category, which included such conditions as normal appendix, carcinoid, oxyuriasis, obstruction, periappendicitis, and catarrhal appendicitis.

From 1947 to 1952 the rate of appendectomy rose rapidly at the Blount Hospital, but the rate of both suppurative and nonsuppurative appendicitis began to fall in 1952. There has been about a 50% decrease in the appendectomy rate in the past 9 years, and this decrease has been associated with a proportionate drop in acute appendicitis as well as other conditions in the appendix. The possibility is suggested that some patients with appendicitis get well without definitive treatment, but, on the other hand, it has been impossible to show that patients who came to operation were being watched longer now than previously. Those suspected of acute appendicitis, but not operated on, did not receive antibotics, which would explain their "cure."

Congenital Absence of the Fibula. A. W. Farmer and C. A. Laurin. J. Bone & Joint Surg. 42A:1-12 (Jan.) 1960 [Boston].

The authors report on 32 extremities with congenital absence of the fibula in 24 patients seen at the Hospital for Sick Children in Toronto between 1931 and 1957. There were 13 boys and 11 girls. The deformity was bilateral in 8 patients. In 16 patients with unilateral absence of the fibula, shortening was always noted in the tibia. Thirteen of these patients also had shortening of the femur. In the dysplasia of the extremity which accompanies congenital absence of the fibula, there is usually shortening of the femur as well as the tibia. Anterior bowing and shortening of the tibia were noted in 17 patients; in the severe cases medial bowing was also present. The tibia was straight in 4 patients who also had partial absence of the femur and in 3 patients with milder deformities (valgus and some shortening of the extremity). The foot was anatomically incomplete in 16 patients. It was always in some valgus position and usually in equinus position as well. In patients with unilateral absence of the fibula, lesions were twice as common on the right side.

Foot deformity, tibial bowing, and discrepancy in length of the extremities are 3 common components which must be considered in treatment. The treatment required must be specific for each patient. Manipulations, applications of plaster casts, and tendon-lengthening procedures for marked foot deformities are followed by recurrence of the deformity unless the foot is overcorrected and maintained in that position. A posterolateral surgical release is necessary when the deformities are severe. In the mild cases the ankle joint is occasionally stable despite absence of the fibula, and in such cases little or no treatment is necessary. Tibial bowing is not affected by weight-bearing and braces. It may regress spontaneously, but will not progress. A tibial osteotomy was performed for severe bowing in 2 patients. The correction obtained at operation in these patients has been maintained during growth to date. Tibial osteotomies will unite. Discrepancy in length of the extremities can be the most important and distressing aspect of this deformity. Early amputation is recommended whenever length discrepancy is expected to be more than 3 in. at the completion of growth. A second indication for early amputation is a severe foot deformity. Seven amputations were performed because of severe shortening. The operation of choice was the Syme amputation, usually modified by preserving the calcaneus and applying it to the lower end of the tibia, much as is done in a Pirogoff amputation. Unlike other end-bearing amputations in growing children, this stump, like a normal heel, is durable and allows growth. If tibial bowing is severe, it should be corrected, preferably by performing a wedge osteotomy. A regular Syme prosthesis is well tolerated by older children, but a pelvic belt and a thigh harness are necessary for infants and young children.

NEUROLOGY & PSYCHIATRY

Experimental Brain Injury and Delayed Hypothermia. H. L. Rosomoff, K. Shulman, R. Raynor and W. Grainger. Surg. Gynec. & Obst. 110:27-32 (Jan.) 1960 [Chicago].

The effects of hypothermia on the pathological character and the mortality of acute brain injury were studied in mongrel dogs, weighing between 10 and 15 kg. (22 and 33 lb.) and unselected as to age and sex. Standardized brain injuries were produced by application of liquid nitrogen in a brass type of cerebral palsy. A high incidence of severe coxa valga, subluxation, and dislocation of the hip is associated with this contracture. Of the orthopedic surgical procedures performed on these patients, 171 were adductor myotomies, all but 14 of which included neurectomy of the anterior branch of the obturator nerve. The results which were obtained in these patients have shown that, in severe scissoring associated with adduction contracture of the hip, an adductor myotomy combined with anterior obturator neurectomy uniformly gives good results, provided that the patient's mental and motor status meet certain requirements. Adequate postoperative management and attention to certain minimum rules of care are major factors in the results. These patients must be followed over a long period of time for a maximum result to be obtained.

Acute Suppurative Arthritis of the Hip in the Neonatal Period. B. E. Obletz. J. Bone & Joint Surg. 42A:23-30 (Jan.) 1960 [Boston].

The author reports on 15 infants in the neonatal period, who were treated for suppurative arthritis of the hip at the Children's Hospital in Buffalo between 1946 and 1956. Of these, 9 were full-term and 6 were premature infants. Septicemia, the precursor to suppuration of the hip joint, is difficult to recognize in patients of this age group; it should be suspected on the basis of the following clinical observations: presence of an open wound or known focus of infection; general observation that the infant is doing poorly; refusal or regurgitation of feeding; cyanosis during feeding; lethargy or irritability; increasing icterus; abdominal distention; appearance of edema in the lower extremities, buttocks, or sex organs; failure to maintain weight or to continue to gain when the infant had already been gaining; rapid fall in hemoglobin level; and rise in temperature. Hemolytic Staphylococcus pyogenes var. aureus was the most common organism recovered from the blood stream and the hip joint. It was found in 5 of the 6 premature infants and in 7 of the 9 full-term infants, including 1 with bilateral hip involvement. In 15 hips hematogenous osteomyelitis of the intracapsular portion of the femur (11 hips) and of the ilium (4 hips) was the source of the joint pus. In the one hip that showed no focus of involvement in the bone, the hemolytic streptococcic infection may have reached the joint by synovial implantation of organisms.

Subluxation or pathological dislocation of the hip was seen on roentgenograms in all the infants in this group. In 12 hip joints infected with hemolytic Staph. pyogenes var. aureus, 8 femoral heads disappeared. In all 8 there was a delay of from 4 to 16 days from the onset of hip joint suppuration to local treatment of the hip, either by surgical drainage or by repeated aspiration and instillations of penicillin. The most important factors in saving the cartilaginous femoral heads in infected hip joints in the neonatal period are early diagnosis and prompt evacuation of pus, preferably by surgical incision and drainage. Systemic administration of antibiotics proved to be effective in controlling septicemia and osteomyelitis, but the antibiotics were unable to sterilize the infected hip joints. Antibiotics could not take the place of surgical drainage.

Recent Experiences with Spontaneously Disappearing Gallstones. H. J. Dworken. Gastroenterology 38:76-86 (Jan.) 1960 [Baltimore].

Gallstones, previously demonstrated roentgenologically, were found to have disappeared at the time of cholecystectomy in 5 patients, 3 of whom were men and 2 were women. Interval cholecystograms had foretold disappearance of the gallstones in 4 patients. Cholelithiasis was closely related to recent pregnancy in the women. One woman and one man had relapsing pancreatitis associated with cholelithiasis. One patient had a questionable history of intermittent pancreatic insufficiency. The stones were quite small and radiolucent in all instances, whereas the gallbladder was able to concentrate the dye.

The initial roentgenologic diagnosis was likely reliable, because 4 patients had subsequent episodes of probable biliary colic. Disappearance of the gallstones was noted in 3 patients in a period of less than one month. This is a rather short time in which to expect complete dissolution of the gallstones in the gallbladder. No fistula was demonstrated at surgery, which rules out the possibility of the gallstones passing through a fistula which later sealed off. However, adhesions around the gallbladder were noted in 2 patients, indicating existence of a recently closed fistula. The most likely explanation of disappearance of the gallstones was that they had passed into the intestine by way of the ductal system before or at the time of surgery. The author suggests repetition of cholecystography before surgery in patients with "known" gallstones, especially if the stones are small or have been associated with recent pregnancy or relapsing pancreatitis.

The Declining Appendectomy Rate. E. P. Kintner. J. Tennessee M. A. 53:14-16 (Jan.) 1960 [Nashville].

During the period between the 2 world wars the emphasis was on the reduction of the mortality and morbidity of acute appendicitis. Early recognition and operation were emphasized, and it was generally accepted that it was better to take a chance on the removal of a normal appendix than to allow a patient with acute appendicitis to go unoperated. With the advent of antibiotics that cortisone. Potassium chloride, 2 Gm., was given daily during the period of cortisone therapy in addition to a normal diet.

Cortisone was given orally in an absolute dose of 300 mg. during the first 24 hours and of 200 mg. during the second 24 hours. Then, 150 mg. of cortisone per square meter of body surface per 24 hours was administered until the tapering-off period, and the dosage of the drug was reduced gradually to zero over a period of 10 to 33 days. Patients who had endocarditis or myocarditis also received acetylsalicylic acid. The sedation did not influence the clinical course of the chorea in these patients, but under the influence of cortisone the motor manifestations of sereve chorea rapidly decreased. The over-all course of the chorea does not seem to be altered by the administration of cortisone, but the author feels that, until a better therapeutic regimen for the treatment of Sydenham's chorea becomes available, cortisone (or possibly the newer steroids), when used as outlined, would seem to be of value.

GYNECOLOGY & OBSTETRICS

Hofstätter's Syndrome: Clinical Aspects in 44 Cases. A. P. Mirra and S. Acquesta. Rev. paulista med. 55:355-361 (Nov.) 1959 (In Portuguese) [São Paulo, Brazil].

Forty-four cases of premenarchal mammary asymmetry (Hofstätter's syndrome) are reported. The patients were examined and treated at the hospital of the Associação Paulista de Combate ao Cancer (Paulista Association of Anticancer Campaign) in São Paulo, Brazil. Their ages ranged from 5 to 13 years. Thirty-four patients had been presented because it was thought they had a tumor; in 6 there was only awareness of the asymmetry in the mammary development; 4 complained of pain. The overdeveloped breast presented a discoid shape with a sharp contour and a smooth surface. The investigation of lymph nodes was negative in 72.7% of the patients. When there were palpable nodes, only the axillary were involved. Thirty-nine patients (88.6%) received no treatment. Two patients received antiphlogistic therapy, 2 were treated with hormones, and 1 was treated with antibiotics.

The diagnosis of Hofstätter's syndrome is exclusively clinical. The importance of a detailed physical examination lies in the differential diagnosis, especially the detection of secondary sexual characteristics. The authors believe that this asymmetrical development does not interfere with the age of menarche, at which time the breasts are equalized, and their development balanced. The main advantage of an early diagnosis is the avoidance of unnecessary, and even harmful, treatment which may be given on the assumption that the overdeveloped breast contains a tumor. The difference in development corresponds to an excessive response of the overdeveloped breast to estrogenic stimuli, rather than an insufficient response of the less-developed breast.

Diagnostic Conization of the Cervix: An Analysis of 235 Operations. J. H. Ferguson and P. E. Demick. New England J. Med. 262:13-16 (Jan. 7) 1960 [Boston].

The technique of conization employed by the authors is designed to minimize trauma to the cervical tissue. No preoperative douche or suppository is used. Anesthesia is either general or spinal. The ectocervix is sprayed with 7% tincture of iodine. A dilute epinephrine solution is injected into the cervix to decrease blood loss. A cold knife is used to excise the cone. The one-piece specimen includes the squamocolumnar junction, the ectocervix that appears abnormal or that does not take the iodine stain well, and at least 1.5 cm., usually 2 cm., of the endocervical canal. After the excision of the cone, curettage of any remaining part of the endocervical canal is performed with a sharp curette. Then, the internal cervical os is dilated, and the uterine cavity is curetted. Bleeding points at the conization site are controlled with a suction-electrocautery instrument. Often, a pack is placed in the cervical defect for 12 to 24 hours. The cone specimens are divided into 12 tissue blocks, and step sections are made from each block. If there has been a positive cytological test, or a confusing histological pattern, more sections are examined.

The authors review their experiences with conization of the cervix in 235 nonpregnant patients. at the University of Miami-Jackson Memorial Hospital in Miami, Fla., over an 8-year period ending on Dec. 31, 1958. The more extensive use of cervical conization is a result of an enlarging program of cytological examination, more puzzling positive cytology reports, and an increase in the number of women with the diagnosis of intraepithelial carcinoma of the cervix. The authors perform the diagnostic conization operation on all women with an unexplained positive cytological test and on all who have had intraepithelial carcinoma of the cervix diagnosed by punch biopsy. They also found it safest not to depend on a punch-biopsy diagnosis of dysplasia as the complete explanation for a positive cytological test, since in many of these patients a more serious diagnosis is revealed in the larger specimen provided by conization. Their observations convinced them that conization is indicated in women with an unexplained positive cytological test (that is, invasive carcinoma has not been found by punch biopsy) and in those in whom a diagnosis of intraepithelial carcinoma of the cervix has been made by punch biopsy. Comparison of cone-biopsy specimens and subcylinder to the surgically exposed dura mater and subjacent brain. A median lethal injury (LD_{50}) was established, which corresponded to a 5.42-mm. lesion from a contact time of 3½ minutes with the liquid nitrogen. The LD_{50} injury killed 50% of the animals at normal body temperature. When this same sized injury was produced in dogs at 26C (78.8F), and the animals were rewarmed after one hour of hypothermia, the mortality dropped to 1 out of 15 dogs. Cerebrospinal fluid (CSF) pressure was measured in normothermic and hypothermic dogs, with and without injuries. There was little change during a 12-hour period at normal body temperature, followed by a decrease under hypothermic control and a return to the precooling level when the normal temperature was reestablished. The average CSF pressure was determined in 3 dogs with brain injuries produced at a body temperature of 25C (77F); after the injury there was a small rise during one hour of hypothermia. After the return to normal body temperature there was an increase, reaching a degree higher than the CSF pressure in the normothermic injured animal. By the 7th or 8th hour both normothermic and hypothermic pressures equalized and remained stable.

LD_{50} lesions were then produced in different groups of hypothermic dogs. At variable intervals after the injury (1 to 12 hours), hypothermia was induced and maintained for 1 hour. If the hypothermia was started within 3 hours after injury, no death resulted after the return to normal temperature. If the delay was longer than 7 or 8 hours, the mortality rate reverted to 50%. CSF pressure measurements under these circumstances indicated a temporary decrease during hypothermia. After rewarming, the CSF pressures paralleled the normothermic injury values. The authors conclude that hypothermia protects against the mortality of experimental brain injury if the temperature is reduced sufficiently early after the injury is produced. No relationship was found between CSF pressure and the degree of cerebral edema and mortality.

Psychological Studies on Effects of Chemosurgery of the Basal Ganglia in Parkinsonism: I. Intellectual Functioning. M. Riklan, L. Diller, H. Weiner and I. S. Cooper. A.M.A. Arch. Gen. Psychiat. 2:22-32 (Jan.) 1960 [Chicago].

The authors report on 66 men and 23 women, between the ages of 31 and 69 years, who underwent chemopallidectomy and chemothalamectomy for the relief of the symptoms of paralysis agitans (Parkinson's disease) at St. Barnabas Hospital for Chronic Diseases and Bellevue Hospital Center in New York. These 89 patients had administered to them the Wechsler-Bellevue intelligence scale, form 1, either preoperatively and postoperatively, or preoperatively and in a long-range follow-up evaluation. For 71 patients scores were available of tests administered before and immediately after basal ganglion surgery, and for 49 patients scores of tests administered preoperatively and postoperatively in a long-range follow-up of 4 to 13 months. The mean postoperative time for the former group was 22.4 days, and for the latter group 9.7 months. Complete preoperative data were available for all the patients, as well as detailed analyses of the specific lesions, made possible through the use of a radiopaque substance. All the patients had unilateral lesions only. From statistical analyses of the data, as well as from the study of individual cases, the following conclusions were drawn concerning unilateral basal ganglion lesions.

The pattern for the group is a general decline in intellectual scores in the immediate postoperative or acute situation, and a return to the preoperative level when evaluated a mean period of 9 months later. In the long-range situation there is a suggestion of slight continuing deficit in verbal functioning for the left-brain group, in the somatic aspects of intellectual performance for the right-brain group, and in motivational energy available for both hemisphere groups. Reality contact is increased. In the immediate postoperative situation those subtests of intellectual fnuctioning most affected are the ones requiring attention, concentration, or a mobilization of intellectual energy. These appear to be related to a temporary physiological change in the brain rather than to any specific organic deficits. The preoperative neurological and mental condition of the patient is of primary significance in determining the differential reactions to brain surgery.

Sydenham's Chorea Treated with Cortisone. T. F. Fletcher. Pennsylvania M. J. 63:63-67 (Jan.) 1960 [Harrisburg].

The author reports on 8 patients who were treated with cortisone in 9 attacks of chorea. During the acute phase of the illness, when the motor manifestations were at a peak, the patients were treated in the pediatric department of the Geisinger Memorial Hospital and Foss Clinic, Danville, Pa. After the acute phase of the illness, they were followed in the outpatient department. Five of the patients had received sedation from their physician, which had not caused any change in the clinical course. After hospitalization they had received moderate or heavy sedation in the form of phenobarbital for periods varying from 2 to 7 days prior to the institution of cortisone therapy. Procaine penicillin, 400,000 units, was given intramuscularly daily for 8 days at the onset of hospitalization. Chlortetracycline, 0.5 Gm. per square meter of body surface per 24 hours, was administered orally while the patients received cardiac catheterization, and surgical exploration, can then be carried out as required, and definitive treatment applied.

Cytomegalic Inclusion Disease of the Newborn: Report of Case with Persistent Viruria. R. C. Kluge, R. S. Wicksman and T. H. Weller. Pediatrics 25: 35-39 (Jan.) 1960 [Springfield, Ill.].

The authors report the first case of cytomegalic inclusion disease in which the virus was isolated during the neonatal period. The patient, a male infant, was born at the U. S. Naval Hospital in Chelsea, Mass., of an 18-year-old mother whose pregnancy had been complicated by several illnesses. The child, whose birth weight was 3,000 Gm. (6.6 lb.), developed jaundice 6 hours after being born. There was a generalized petechial rash, especially marked about the head and face. On physical examination hepatosplenomegaly was noted. On the 5th and 8th days of life the urine sediment was found to contain epithelial cells with prominent eosinophilic, intracytoplasmic inclusion bodies. On the assumption that the inclusion-bearing cells in the urine were the result of a viral infection, specimens of blood, urine, and cerebrospinal fluid were inoculated into tissue cultures on the 14th day of life. Cytomegalic virus was recovered from the urine sediment. The jaundice and purpura subsided, while the hepatosplenomegaly increased in degree. A 60-ml. blood transfusion was given, because the concentration of hemoglobin had fallen to 8.5 Gm. per 100 cc. The infant was discharged at one month of age, weighing 3,500 Gm. (7.7 lb.).

The child appeared to be developing well at 36 days of age; at 3 to 4 months it was evident that there was motor retardation. Cytomegalic virus was again recovered from the urine at 3, 16, 21, and 26 months of age. At the same time, neutralizing antibody for the virus was present in the patient's serum. The child's condition improved gradually; the spleen was no longer palpable, and the hepatomegaly was less marked. The patient was last seen at 26 months of age; he was active and alert, although his speech ability remained poor. The recovery of cytomegalic virus from the urine, as demonstrated in this case, needs to be interpreted with caution. A demonstrable viruria may reflect an infection acquired months prior to the time of isolation of the virus.

Antibiotics in the Treatment of Beta-Hemolytic Streptococcal Pharyngitis: Factors Influencing the Results. M. Stillerman, S. H. Bernstein, M. L. Smith and others. Pediatrics 25:27-34 (Jan.) 1960 [Springfield, Ill.].

Throat cultures were taken from 410 children with respiratory illness suspected of being caused by beta-hemolytic streptococci. Those severely ill were immediately treated with penicillin, and if the cultures were positive, the therapy was continued, either with penicillin V given orally for 10 days or with one intramuscular injection of benzathine penicillin. Penicillin V and potassium penicillin V were given in daily oral doses of 375 to 750 mg. (600,000 to 1.2 million units), respectively; benzathine penicillin G was injected once intramuscularly in a similar dose. Patients allergic to penicillin and those in whom a streptococcic infection was not recognized at the initial examination received erythromycin and tetracycline orally in daily doses of 30 to 50 mg. per kilogram of body weight up to 1 Gm. The results of the treatment were evaluated on the basis of the throat cultures. The patient was considered cured when the cultures were negative after the 5th day of treatment and one or more cultures were negative for 18 to 60 days. A positive culture on the 6th to the 10th day of therapy meant failure. A relapse was indicated by a recurrence of positive cultures 11 to 60 days after starting the treatment. Reinfection meant a positive culture yielding streptococci of a different serologic group and type from the initial isolate.

The bacterial cure rate was 84% for 224 patients treated with penicillin V and potassium penicillin V and 86% for 129 patients treated with benzathine penicillin G. The cure rates were 48 and 38%, respectively, for 23 patients treated with erythromycin and 34 patients treated with tetracycline. The occurrence of 15% of relapses and/or failures, in spite of the recommended regimen of penicillin, suggests that, among other factors, reexposure to streptococci of homologous serologic type may produce reinfection. Complications during the therapy were one case of otitis media and one of glomerulonephritis, which developed 12 and 22 days, respectively, after the onset of the treatment. The data indicate that penicillin was more effective than erythromycin and tetracycline in eradicating beta-hemolytic streptococci from the host.

UROLOGY

Periureteral Fibrosis, with a Diabetes Insipidus-like Syndrome Occurring with Progressive Partial Obstruction of a Ureter Unilaterally. D. Knowlan, M. Corrado, G. E. Schreiner and R. Baker. Am. J. Med. 28:22-31 (Jan.) 1960 [New York].

The authors report on 3 men, between the ages of 44 and 75 years, with periureteral fibrosis, who underwent plastic surgical procedures at Georgetown Hospital in Washington, D. C. The first patient was admitted to the hospital with a history of polydipsia and polyuria of 3 weeks' duration and a tentative diagnosis of diabetes insipidus. Impaired concentrating capacity, poor response to vasopressin (Pitressin), and renal hypertension suggested damage to the nephron with progressive obstruction to the urinary tract, similar to that reported sequent hysterectomy specimens revealed that wide conization cannot always be depended upon to remove completely the neoplastic tissue.

PEDIATRICS

Transmission of Hospital Staphylococci Among Newborn Infants: I. Observations on the Contamination of a New Nursery. V. Hurst. Pediatrics 25:11-20 (Jan.) 1960 [Springfield, Ill.].

A study of environmental staphylococcic contamination of newborn infants was made in the newly opened nursery of the Herbert C. Moffitt Hospital in San Francisco. Fourteen infants within the first 4 days of life and 9 members of the nursing staff were transferred to the new nursery from the old one in the University of California Hospital. The investigation, which had begun in the old nursery some months before, was continued in the new one for another 5 months. There were 2 new units for full-term infants. The personnel wore masks in unit B only during the first month, and in unit A only during the second month. Admissions were allocated alternately between the 2 units in order to equalize the 2 infant populations. Air samples were collected in the old nursery and in the new one both before and after its opening. Five of the personnel members transferred from the old nursery and 4 of the new persons added to the staff were carriers of staphylococci. Nasal and throat cultures obtained from the 4th day of life until the day of discharge (and later also cultures from the umbilical cord) were used as indexes of infant colonization.

Neither the more desirable physical plan of the new nursery nor the masking of the nurses affected the carrier rate of infants. The average incidence of isolation of staphylococci among infants of the new units was 43% when the nurses wore masks and 44% when they did not wear masks. Phage typing of the staphylococci from infants born approximately one month prior to and one month after the opening of the new nursery revealed that the colonization was by similar strains in both nurseries. The 14 infants transferred from the old nursery acquired staphylococci at a rapid rate. Eight of 22 infants who became contacts of the transferred children became carriers. All staphylococci isolated from the infants differed from those of the staff member carriers. No staphylococci were recovered from the air of the new nursery during the week before its opening, but on the opening day the count rose quickly to the level in the old nursery. In the following 9 weeks the average staphylococcic count in the new nursery, as compared with the old one, was only slightly lower, although the total bacterial counts averaged less than half. The staphylococcic count in the corridor air was approximately one-third of the count in the nursery units, although the total bacterial counts were similar. The findings indicate that newly born infants derive their staphylococci primarily from older infants. Hospital nurseries may have to be replaced by rooming-in units specifically designed to meet present-day epidemiologic problems.

Congenital Absence of the Aortic Arch. P. Fournier and Z. H. Zaidi. Am. Heart J. 59:148-152 (Jan.) 1960 [St. Louis].

The authors report on a 3-week-old female infant who was admitted to the department of pediatrics of the Ottawa General Hospital because the liver and spleen were palpable and the patient was thought to be in early heart failure. A posteroanterior roentgenogram of the chest, which had been taken shortly after birth, showed a slightly enlarged heart. A gallop rhythm became apparent, and there was roentgenologic evidence of pneumonia. An electrocardiogram suggested left ventricular hypertrophy with abnormal T wave and S-T segment, consistent with interventricular septal defect. After 13 days the infant was discharged, her hospital course having been punctuated by bouts of cyanosis. She continued to nurse poorly at home and became emaciated; respiratory distress developed, and the patient died at the age of 2 months. Autopsy revealed that the aortic arch was interrupted distal to the left subclavian artery. There was hypoplasia of the ascending aorta, patent but stenotic ductus arteriosus joining the pulmonary artery to the descending aorta, an interventricular septal defect, a bicuspid aortic valve, dilatation of the right atrium and ventricle, and hypertrophy of the wall of the right ventricle.

Thirty-nine cases of complete absence of the aortic arch were collected from the literature. This congenital anomaly is the result of a minute caudal displacement of the heart and obliteration of the 4th left aortic arch, which in the adult normally develops into that part of the aorta lying between the left subclavian artery and the insertions of the ductus arteriosus. The ductus arteriosus, originally the 6th left aortic arch, persists to supply the descending aorta with blood from the pulmonary artery. The physiological and clinical findings resemble those of severe preductal coarctation with a patent ductus arteriosus and pulmonary hypertension. Since surgical techniques are now available for correcting absence of the aortic arch, the recognition of this condition becomes of great importance. One of the main clinical observations, within reach of all who are aware of it, is to determine the presence of differential cyanosis between the upper and lower extremities, and occasionally of unilateral cyanosis of an upper extremity, simply by placing one extremity beside the other and noting variation in color. More elaborate studies, such as angiocardiography, aortography, The response to therapy was considered good in 4 of the 7 patients with pulmonary coccidioidomycosis and excellent in the one patient with disseminated blastomycosis. These 5 patients showed physical and symptomatic improvement after treatment; cultures were negative, and roentgenographic findings were improved in each case. One of these 5 patients had a recurrence 10 months after termination of treatment, as revealed by culture findings. The response to therapy was considered poor in one of the remaining 4 patients. This patient had coccidioidomycosis. The size of the cavity had decreased and the sputum had become negative for Coccidioides immitis, but a recurrence, as revealed by culture findings, occurred 2 months after termination of treatment. Two patients who had pulmonary coccidioidomycosis were given amphotericin B for 4 weeks prior to surgical resection of their primary lesions to prevent local recurrence of the disease during the postoperative period. Although neither developed this complication and were well 10 months after termination of treatment, it was not possible to determine the value of amphotericin B in the management of their disease. The patient with histoplasmosis, who had concomitant extensive parenchymal disease and fibrous mediastinitis, did not respond to treatment with amphotericin B.

Proteinuria and cylindruria were frequently noted during the course of therapy. Of interest is the significant elevation of blood urea nitrogen value, which occurred during each course of therapy. More elaborate urinary function tests showed an inability to concentrate urine, to excrete phenolsulfonphthalein dye, and to clear blood urea and creatinine concentrations during therapy. All renal abnormalities cleared after the completion of therapy. Acute toxic reactions frequently occurred during the period of intravenous infusion of amphotericin B. The severe reactions occurred during the first weeks of administration, and subsequent reactions were of decreasing severity. There were no residual clinical stigmas after completion of therapy.

The Preventive Effect of Ephedrine in Syncopal Accidents Caused by Quinidine: A Study on 300 Cases of Regularization of Atrial Fibrillation. F. Liot, B. Coblentz, L. Scebat and others. Arch. mal. coeur 52:1321-1336 (Dec.) 1959 (In French) [Paris].

Severe accidents, at times fatal, constitute the major problem in the treatment of atrial fibrillation with quinidine. The authors report on a series of patients with atrial fibrillation who were treated with dihydroquinidine and, in addition, were given 0.01 Gm. of ephedrine for every 0.30 Gm. of dihydroquinidine. This combination was used 300 times among 262 patients. No deaths were observed in this series; previous statistics showed a mortality rate of from 0.6 to 10.9%. Two instances of syncope and 5 of benign lipothymia were observed in the series reported. The authors point out that the severe accidents caused by quinidine are observed after the return of the sinus rhythm, which occurs often in cases of disturbances of the atrioventricular conduction. It is advisable to continue the administration of ephedrine after the return of the sinus rhythm and not to interrupt it until the patient has been put on a maintenance dose of dihydroquinidine. The existence of a nodal rhythm noticed in 6 patients during regularization of fibrillation, which was replaced by a sinus rhythm when dihydroquinidine was withdrawn, confirms the depressive effect of this drug on the sinus node, as well as the preventive role that ephedrine can play against syncopal accidents.

Heparin in Acute Myocardial Infarction: Observations Indicating the Potential Advantages of Using It as the Sole Anticoagulant in Therapy. H. Engelberg. California Med. 91:327-331 (Dec.) 1959 [San Francisco].

There is a considerable body of experimental evidence that heparin is superior as an anticoagulant to any prothrombin-depressing drugs. Furthermore, its lipemia-clearing action affords other benefits which result from the removal of fat from the blood stream. Important among these beneficial effects is the increased tissue and myocardial oxygen consumption, which results from the injection of heparin in atherosclerotic patients. The results of a study made on 2 groups of patients, the first group being composed of 100 patients treated with heparin alone for 3 weeks and the second consisting of 63 patients treated with heparin for 2 or 3 days and then with bishydroxycoumarin (Dicumarol), showed that 28 patients (28%) of the first group died while 24 (38%) of the second group died. The superiority of heparin was substantiated by the findings in the most seriously ill patients, those with 3 or more complications on admission. In these subjects the mortality rate was significantly different; 14 (23%) of 60 patients treated with heparin alone and 11 (58%) of 19 patients treated with heparin and Dicumarol died.

With regard to the administration of heparin, the author suggests that a 50-mg. or a 100-mg. dose should be injected intravenously; intramuscular administration is likely to be painful or to produce ecchymosis, when the diagnosis of infarction is made in order to attain full anticoagulant activity immediately. Subsequently, if the patient is receiving continuous intravenous therapy, 50 mg. of heparin should be given in the infusion tube every 4 hours. This method requires infrequent laboratory controls. If continuous intravenous drip is not being employed, subcutaneous injection is preferred. In nearly all patients 150 mg. of the concentrated aqueous heparin every 12 hours subcutaneously affords excellent maintenance of anti-after release of obstruction. Three years previously the patient had undergone nephrectomy for an adenocarcinoma of the left kidney. Biopsies taken on adjacent structures at the time of the nephrectomy revealed fibrocytic proliferation but no tumor tissue. Upon recurrence of symptoms 3 years later, attention was first given to the possibility of contralateral spread of metastases from the hypernephroma. Instead, an unusual case of ureteral obstruction was found to arise from spread of fibrocytic proliferation from the anterior and posterior leaves of the renal fascia, with the formation of a vise-like cuff, several centimeters thick, around the upper third of the ureter, which itself was not invaded by the fibrocytes. When the ureter was stripped free of its vise-like sheath, there appeared to be no disturbance of ureteral function.

Periureteral fibrosis is conceived to be an exaggerated fibrocytic response to varied stimuli. In the first patient the adenocarcinoma was probably responsible. In the other 2 patients the fibrocytic proliferation seemed to be a response to chronic ureteritis and smoldering pyelonephritis. In one of these patients the ureter itself was involved in the fibrocytic proliferation, and plastic surgery involved the bridging of an unusually long segment of diseased ureter by regeneration of the ureter around a splinting catheter. Plastic surgical procedures made rehabilitation possible in all 3 patients.

Twenty-four additional cases of periureteral fibrosis were collected from the English literature. Clinically, the condition appears to predominate in middle-aged men, who usually have a history of vague back pain or abdominal pain of several months' duration, which is usually progressive and associated with nausea, vomiting, weight loss, and malaise. In 40% of the cases the patients subsequently became anuric. Anemia was a constant feature. Retrograde pyelography, after abnormal intravenous pyelograms, revealed bilateral involvement in 50% of the patients. Hydronephrosis or ureteral obstruction was found. The patients underwent surgery, initially nephrectomy or nephrotomy, with ureterolysis on one side, and subsequently an operation on the other side with freeing of the ureter. The postoperative course varied. The patients usually became symptom-free and without abnormal findings. Only 3 of the 24 patients died. It appears that freeing of the ureter bilaterally might be all that is necessary for satisfactory results. When direct ureteral involvement is present, the newer plastic procedures have much to offer.

Periureteritis Fibrosa (Gerota's Fascitis). F. Lund and J. Pedersen. Ugesk. læger 121:1853-1856 (Nov. 26) 1959 (In Danish) [Copenhagen].

Periureteritis fibrosa is a well-defined, rapidly progressing disease whose pathological manifestations develop within *Gerota's* fascia perirenalis. Death is caused by uremia. The first case of acute anuria from bilateral renal compression due to a retroperitoneal fibrous connective tissue formation was reported in 1948; 26 such cases have now been reported. Men in their 40's are most often affected. The invasive fibrosis, with varying degrees of inflammatory reaction, is histologically dominated by lymphocytes and plasma cells. No primary infectious focus has been demonstrated. The disease is not usually accompanied by fever, and regional enlargement of lymph nodes has not been described. Neither stasis nor signs of arterial insufficiency appear in the lower extremities. Intravenous urography most frequently suggests the correct diagnosis. In the cases described, treatment has been surgical. Early diagnosis, before symptoms from the urinary tract develop, is most important, so that there may be a chance of arresting the process by medicamental means. At this early period diagnosis often has to be made by exclusion and after exploratory laparotomy. When the objective findings are so characteristic that diagnosis is not difficult, recovery is hardly possible. For the present the disease must be classed among the collagenoses, with therapy based on corticotropin (ACTH), corticosteroids, and phenylbutazone (Butazolidin). In the case described, in a 44-year-old man, the diagnosis was made before symptoms from the ureters developed. Treatment with Butazolidin has apparently had good effect, and operation on the ureters can perhaps be avoided.

THERAPEUTICS

The Treatment of Deep Mycotic Infections with Amphotericin B: With Particular Emphasis on Drug Toxicity. H. W. Beard, J. H. Richert and R. R. Taylor. Am. Rev. Resp. Dis. 81:43-51 (Jan.) 1960 [New York].

The authors evaluated the therapeutic efficacy and the physiological toxicity of amphotericin B, a new polyene antifungal antibiotic, in the treatment of deep mycotic infections. Seven patients with chronic pulmonary coccidioidomycosis, one patient with disseminated blastomycosis, and one patient with chronic pulmonary histoplasmosis were treated with amphotericin B at Fitzsimons Army Hospital in Denver between March, 1957, and April, 1959. The duration of the disease prior to therapy ranged from 6 months to 8 years, with an average duration of 3 years. In each case, the disease was identified prior to therapy by culture or by examination of tissue sections. Amphotericin B was administered daily in 6-hour intravenous infusions in a dose of approximately 1 mg. per kilogram of body weight for periods of 4 to 6 weeks. The calculated daily dose of amphotericin B was given in a liter of 5% dextrose in water. All laboratory determinations were repeated at 2-week intervals throughout hospitalization.

were among the least susceptible to that antibiotic. The recent strains were nearly all highly or moderately susceptible to sulfadiazine. Comparisons of these results with those reported by other workers from the same laboratory in previous years showed no evidence of any large decrease in susceptibility of gonococci to any of the antibiotics that have been in use during the past few years.

Lesions of Myocardial Fibrosis Occurring in the Course of Fibrocystic Disease of the Pancreas. C. Nezelof and P. Lancret. Arch. franç. pédiat. 16:1035-1046 (no. 8) 1959 (In French) [Paris].

Among 44 patients with fibrocystic disease of the pancreas studied at the Hospital for Sick Children in Paris, the authors observed 2 girls, aged 18 months and 24 hours, respectively, and an 8-month-old boy with extensive and isolated fibrosis and marked vascularization, predominantly of the middle part of the myocardium and involving likewise the 2 ventricles and the septum. A 4th patient, an 8-month-old girl, had subendocardial islets of muscular necrosis. Marked cardiorespiratory failure resulted in the death of all 4 children. Autopsy was performed on all, revealing fibrocystic disease of the pancreas. Macroscopic examination of the cardiac lesions showed that the volume of the heart was increased, particularly on behalf of the left ventricle. Microscopic examination revealed that the fibrotic lesions were not associated with any malformation or with any changes in the endocardium.

The cause of these lesions of the myocardium is not clear. The authors reject the concept of a primary cardiac or coronary disease or of an "idiopathic myocardial sclerosis in childhood." They also do not accept a toxic origin. Only one of the 4 patients was given trypsin, and, therefore, this drug could not have been responsible for the myocardial fibrosis. The authors consider the myocardial lesions as one of the localizations of the fibrocystic disease of the pancreas and as a manifestation of vitamin deficiency rather than of a metabolic disturbance. A vitamin B_1 deficiency has been particularly considered by other workers because of anatomicoclinical observations similar to those in infants with beriberi. This deficiency could be related to the disturbance of the intestinal flora frequently associated with fibrocystic disease and to prolonged treatment with antibiotics.

Study on Causation of Hospitalism Due to Staphylococci: Determination of Germs in the Air of Operating Rooms. H. Göpel. Chirurg 30:529-533 (Dec.) 1959 (In German) [Berlin].

The author used the sedimentation technique in an attempt to test the pollution of the air in the operating rooms of 3 large clinics (A, B, and C) in Berlin. To obtain comparable values, one blood agar plate was exposed for one hour per 3 sq. m. of floor space in the operating rooms. The very modern operating room in clinic A was equipped with a high-pressure air-conditioning apparatus, and the air volume was changed about 6 to 8 times within one hour; everybody who entered the room had to wear protective clothing. The operating rooms in clinics B and C had no air-conditioning apparatus; everybody who entered the operating room in clinic B had to wear protective clothing, while in clinic C only the surgeons wore protective clothing. The largest number of persons present at the same time was 8 in operating room A, 26 in operating room B, and 24 in operating room C. The first test was performed at the start of the day during which operations were performed, it was repeated after an interval of an hour, and a third test was performed after another hour. Thus, the initial value of the air pollution and its increase during the course of operations were determined. The exposed agar plates were incubated at a temperature of 37 C (98.6 F.) for 24 hours and then were exposed to daylight for 24 hours. The colonies which had grown were counted and recorded.

The results showed that the increase in the number of germs in the course of one day was about the same in all 3 operating rooms, but there were considerable differences concerning the total number of these micro-organisms. Operating room C showed a greater number of germs at the start of the tests than operating room A after a 5-hour test period. There are various reasons for these differences, but the number of persons present in, or passing through, the operating room is to be considered an essential factor. Although the air conditioning in operating room A did not prevent the absolute increase in the room pollution, the relatively small number of germs found in this operating room was, at least partly, the result of the air conditioning. All test-plates in operating rooms B and C became remarkably dusty, as observed on macroscopic examination, while only a little dust was observed on the plates in operating room A.

Staphylococcus pyogenes var. albus was the most frequently observed pathogenic agent. Sarcina organisms, spore-forming aerobes, gram-negative saprophytes, and molds were also found, but hemolytic Staph. pyogenes var. aureus was found rarely and only in single colonies. The pollution of the air in the operating rooms tested represents a latent, but not an acute, risk. Further testing of the air in operating rooms is desirable for an exact clarification of the problem and for making improvements possible. Particularly in planning new operating rooms and in the rebuilding of old ones, specific consideration should be given to air hygiene. Important is the exclusion of the outside world, and occasionally the creation of locks.

coagulation effect. In the first 2 or 3 days after infarction a larger dose may be used in some patients. After the first 3 or 4 days a dose of 100 to 125 mg. every 12 hours suffices. During the first 2 days it is advisable to measure clotting time once daily by the Lee-White method, just before the next scheduled administration of heparin, to check on the adequacy of the dose. Once a stable anticoagulant level is reached, it is not necessary to determine clotting time so frequently; once or twice a week is enough.

Observations on Chimpanzees After Whole-Body Radiation and Homologous Bone Marrow Treatment. H. Rothberg, E. B. Blair, A. C. Gomez and W. McNulty. Blood 14:1302-1321 (Dec.) 1959 [New York].

The authors performed homologous bone marrow experiments on the chimpanzee, a higher primate with dimensions comparable to those of a human being. Three chimpanzees were given 900 r of whole-body irradiation, followed within 28 to 33 hours by transfusion of homologous bone marrow. Two animals died within 2 weeks after the bone marrow infusion, but the third survived for nearly 6 months. Autopsies were performed on all 3 chimpanzees, but there was no positive evidence for survival of the transplanted marrow. The authors are inclined to think that the antibiotics administered from the 21st to the 33rd day after the bone marrow infusion to the chimpanzee with the longest survival time contributed more to the animal's welfare than did the bone marrow treatment. Five additional chimpanzees were given 1,200 r of whole-body irradiation, and 3 of them were given homologous bone marrow. There was no difference in survival time between the treated animals and the contratest animals. Observations were made on clinical, hematological, bacteriological, and pathological aspects of irradiation injury.

The experiments were performed under nearly ideal conditions, at least in terms of irradiation dosage and marrow dosage, but there was no good evidence of a successful marrow graft in any of the 6 animals which received bone marrow transfusions. It seems likely that, until one has a clearer understanding of the mechanisms of graft rejection and of the means to circumvent rejection responses, both early and late, one will fall short of the goal of homotransplantation.

PATHOLOGY

Susceptibility of Hemophilus Influenzae to 21 Antibiotics in Vitro. H. A. Hirsch and M. Finland. Am. J. M. Sc. 239:33-40 (Jan.) 1960 [Philadelphia].

The authors tested strains of hemophilus influenzae, which were isolated early in 1959, mostly from the respiratory tract of patients hospitalized at the Boston City Hospital, for in vitro susceptibility to 21 antibiotics, including several that had been employed previously for similar tests on strains of H. influenzae isolated in 1954 and 1949, and also several groups of related antibiotics. The results of the tests showed that all the antibiotics were roughly similar in their activity against these organisms, except bryamycin and some of the erythromycin-like antibiotics, which were much less active, and penicillin, which was more active than all the others against more than one-half of the strains. The results obtained with the strains isolated in 1959 were similar to those obtained with some of the same antibiotics in the 2 earlier studies. In both of the latter all the strains tested were found to be resistant to bacitracin, which was not included in the present tests.

It may be concluded that there has been no significant change in the antibiotic susceptibility of strains of H. influenzae isolated in the Boston City Hospital during the past 10 years. Most of the newly introduced antibiotics are about as active against H. influenzae as those that were previously available, but some of the erythromycin-like antibiotics, namely, carbomycin, oleandomycin, spiramycin, and leukomycin, are much less active. Colimycin appears to be slightly less active than polymycin B; the 4 tetracycline analogues all have similar activity; and there are only slight, and probably not significant, differences in the activity of streptomycin, neomycin, kanamycin, and paromomycin against strains of H. influenzae.

Susceptibility of Gonococci to Antibiotics and Sulfadiazine: A Study of Strains Isolated at Boston City Hospital from Cases of Acute Gonorrheal Urethritis in Males, August, 1958, to February, 1959. H. A. Hirsch and M. Finland. Am. J. M. Sc. 239:41-50 (Jan.) 1960 [Philadelphia].

The authors tested strains of gonococci, which were isolated in pure culture from the purulent urethral discharge of male patients at the genitourinary clinic of the Boston City Hospital between 1958 and 1959, for sensitivity to 20 antibiotics and sulfadiazine. The results of these tests showed that, with the exception of penicillin and sulfadiazine, each of the agents inhibited all the strains of gonococci tested within a fairly narrow range of concentrations, which varied only twofold or fourfold from the median. The inhibiting concentrations of penicillin and sulfadiazine varied for each of these 2 agents over a more than 200-fold range. Different antibiotics varied quantitatively in their activity, but there were only minor differences in the susceptibility of the strains to chemically related antibiotics, except in the case of those related to erythromycin, which varied quite widely in their activity. Strains isolated from patients after treatment with a single dose of 600,000 units of penicillin social and economic factors as standards of living and diet are emphasized throughout the book and particularly in connection with the causation of pelvic contraction, dystocia, the toxemias, premature birth, and maternal mortality. The sections which deal with these relationships represent much advanced thinking and include a wide variety of data that can be found nowhere else. These discussions give the book a new outlook and should be valuable in helping the student to approach obstetrics and gynecology with a broad perspective. The clinical policies set forth are in keeping with the best modern thought and concur with teachings and practices in this country. Hence, the popularity which this volume has so long enjoyed need not be limited to the British Commonwealth, for students as well as practitioners in the United States should find it a lucid, practical, modern textbook of high quality.

Hormone: Einführung in ihre Chemie und Biologie. Von Dr. Ing. Oldřich Hanč. Den Abschnitt über Analyse der Steroidhormone in biologischem Material bearbeitete Ph Mr. Oksana Siblíková. Cloth. 40 marks. Pp. 633, with 9 illustrations and inserts in back pocket. VEB Gustav Fischer Verlag, Villengang 2, Jena, East Germany, 1959.

This is the first German edition of a work which was published in 1953 in the Czech language and has since been thoroughly revised to keep pace with rapid progress in the field. While the author is a pharmacologist and chemist, the clinical implications of the material have not been overlooked. A section on clinical applications has been included at the end of each chapter or subdivision. Of particular value are lists of commercially available preparations of the various hormone groups, with their copyrighted names, their chemical composition, and the names and countries of their manufacturers. These lists can be of practical value to American clinicians in studying the foreign literature as well as in evaluating medicaments that patients bring home from travels abroad and sojourns in European health resorts.

In his introductory chapter the author stresses his preoccupation with the chemistry of hormones and includes a discussion of the basic principles of internal secretions for readers without a medical background. Here is a short section on the hormones of invertebrates, an area that has begun to interest scientists only in the past 20 years. The author is optimistic about the value of further research in clarifying problems of comparative physiology.

The work is divided into three main divisions dealing with hormones that have a tyrosin-like structure, the steroid hormones, and hormones with a peptide structure. The greatest amount of space is given to the steroid group, which is discussed under androgen, estrogen, and corticoid headings. In a special section, O. Siblikova discusses the determination of steroid hormones in biological material. This book is highly recommended to German-reading endocrinologists who are concerned with the fundamental chemical and biological aspects of internal secretion. Of particular interest are the two final chapters which deal with hormones and enzyme systems and with hormones and malignant tumors. The discussion of these two areas opens up wide perspectives for future developments in biochemistry.

F. D. Zeman, M.D.

Anatomy and Physiology of Speech. By Harold M. Kaplan, Head, Department of Physiology, Southern Illinois University, Carbondale. McGraw-Hill series in speech. Clarence T. Simon, consulting editor. Cloth. $8.50. Pp. 365, with illustrations. McGraw-Hill Book Company, Inc., 330 W. 42nd St., New York 36; 95 Farringdon St., London, E. C. 4, England; 253 Spadina Rd., Toronto 4, Canada, 1960.

This new textbook was designed specifically for the student and teacher of speech pathology. It attempts to fill the long-felt need for a single textbook in the broad area of the organic bases of speech. This book should find its way into the library of students of speech pathology and should serve as a reference book in which one can find discussions of anatomy, physiology, neurology, and comparative anatomy. It should be of help to the otolaryngologist and to the physician who desires more specific knowledge about the complex activity of speaking.

This book provides a certain amount of basic information on anatomy and physiology of the speech mechanism and should be of great use as a basic textbook in departments of speech correction. There are a number of deficiencies in the organization and presentation of the material. Much of the text might be called an outline of anatomy and physiology. Numerous statements on the history and development of anatomy and physiology as a science are interspersed. There are sections on neurology and occasional statements about function. Although the author states that this is not a textbook which concerns itself with the treatment of speech problems, he does, from time to time, comment on anatomic and physiological dysfunction and possible effects on speech with implied corrective procedures, as in the discussion on page 257 about the tongue as an articulator.

The table of contents gives the general outline of this book. The author begins with a general discussion of anatomy and physiology followed by a description of the speech mechanism starting with the respiratory system. The systems involved in the production of speech are discussed separately, but there is no final summary of the complex art of articulate speech. The author assumes that the reader has a certain amount of basic information about chemistry, biology, and physics. Few speech undergraduates can be expected to have the amount of information necessary to read the

BOOK REVIEWS

Management of the Aged Surgical Patient. By Sidney E. Ziffren, M.D., Professor of Surgery, State University of Iowa College of Medicine, Iowa City. With chapters on anesthesia by Stuart C. Cullen, M.D., Professor and Head, Department of Anesthesia, University of California School of Medicine, San Francisco; urology by Rubin H. Flocks, M.D., Professor and Head, Department of Urology, State University of Iowa College of Medicine; and discussion of cardiac and diabetic patient facing emergency operation by Raymond F. Sheets, M.D., Associate Professor, Department of Internal Medicine, State University of Iowa College of Medicine. Cloth. $7.50. Pp. 219, with 30 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1960.

This book dealing with all phases of the management of the aged surgical patient is exceptionally well written and completely understandable. It is only a little more than 200 pages long, is readily readable, and is printed on excellent paper. Nothing is omitted which might be of value to those not experienced in operating on aged persons. The preoperative preparation is described in detail, and the postoperative period and its complications are set forth in a clear, concise, and orderly manner.

The special chapters on anesthesia and urology add much to the value of this volume, as does the discussion of the cardiac and diabetic patient facing emergency operation. The book is not profusely illustrated as the need for illustration in a book of this nature is not great, but where they can be of value they do appear and are well done, accurate, and informative. Every surgeon should read, or at least have access to, this book, and the surgeon who deals with patients over 65 years of age should have it in his library for quick reference.

Although the book contains no startlingly new information, it sums up all facts and information regarding the management of the aged surgical patient, whose care differs radically, in many respects, from that of the younger patient. In his preface the author asks, "Why do we need a volume on geriatric surgery?" He goes on to state that "the answer lies in the fact that although the principles of surgical technique are the same in all age groups many facets of surgical diagnosis and care are markedly different in the aged patient in contrast to the younger patient." With the increasing number of aged in our population, a growing demand for surgical care in this group is inevitable; therefore, Dr. Ziffren's book is a most valuable addition to our literature.

David B. Allman, M.D.

Acute Cardiac Pulmonary Edema. By Sigmund Wassermann, M.D. Cloth. $4.25. Pp. 123. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., Blackwell Scientific, Publications, Ltd., 24-25 Board St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1959.

This small monograph brings back into focus and presents in English an important mass of physiological literature that has been rather inaccessible and somewhat neglected in present day reports on pulmonary edema. It represents the reviewing and digestion of a great number of papers. Emphasis is placed on clinical observation of pathophysiological phenomena by a keen clinician who has contributed much to the subject. Excellent case studies are included. The subject of carotid sinus pressure effect in dramatically interrupting attacks is elaborated on. The purely clinical approaches with discussion in detail of the symptoms and signs and a thorough review of the cardiorespiratory, bronchial, and vasopulmonary reflexes and nervous pathways are most refreshing. This monograph is well worth study by every active internist. There is an index and a list of reference.

George R. Herrmann, M.D.

Combined Textbook of Obstetrics and Gynæcology for Students and Practitioners. Edited by Dugald Baird, B.Sc., M.D., D.P.H., Regius Professor of Midwifery, University of Aberdeen, Aberdeen. Sixth edition. Cloth. $15. Pp. 936, with 492 illustrations. Williams & Wilkins Company, 428 E. Preston St., Baltimore 2; E. & S. Livingstone, Ltd., 7 and 8 Teviot Pl., Edinburgh 1, Scotland, 1957.

This is a new edition of a work which has served well the needs of medical students and practitioners throughout the British Commonwealth for over 35 years. The editor, with the assistance of 12 contributors, has extensively revised the previous edition. This is essentially a textbook, and as such it is a fine example of that great desideratum of all textbooks, namely, clarity. This has been achieved by orderly arrangement of the subject matter, by a simple, concise style of writing, and by a wealth of informative illustrations, tables, and charts. Medical students should find this book easy and interesting reading. From the viewpoint of the practitioner, the management of the various pathological conditions surveyed is sufficiently detailed and specific to provide valuable reference material.

Although the basic approach to the subject is the same as in previous editions, special consideration is given to preventive measures as an integral part of obstetrics and gynecology. For example, such problem; what the limitations of radiologic investigation are; and how unnecessary procedures may be avoided. On the other hand, the specific problems with which the surgeon is concerned in diseases of internal organs are brought to the attention of the radiologist in every chapter. The diseases discussed include those of the salivary glands, pharynx, thyroid, diaphragm, all organs of the chest and abdominal cavity, peripheral vessels, and urinary system. The chapter on the heart and large endothoracic vessels is focused on the needs of the cardiac surgeon in the modern therapeutic approach to congenital anomalies and describes briefly the various modern cardioangiographic methods.

A discussion of neurosurgical problems was omitted because this field has become distinctly separated from the realm of general surgery. The book contains an index of the second volume, which is not yet available. The index indicates that the second volume deals with the diagnosis of diseases of the skeletal system and of the soft tissues of the extremities and that it is written by the two surgeons. If the second volume matches the first in the wealth of information and the beauty of the illustrations, the authors and publisher deserve high praise.

PHILIP THOREK, M.D.

Autoogenous Vein Grafts and Related Aspects of Peripheral Arterial Disease. By W. Andrew Dale, M.D., Assistant Professor of Clinical Surgery, Vanderbilt University School of Medicine, Nashville. With preface by Earle B. Mahoney, M.D. Cloth. $6. Pp. 123, with 32 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1959.

This monograph consists of a review of the diagnosis and treatment of segmental occlusions of the iliac and femoral arteries, with emphasis on the latter. Techniques of arteriographic examination, surgical procedures, and attendant complications are discussed. Primary emphasis is placed on an extensive laboratory and limited clinical experience with and the use of autologous vein grafts to replace or bypass segments of small vessels. It is concluded that aneurysmal dilatations of autologous vein grafts are relatively rare, contrary to the impressions held by many. Some dilatation is common but occurs early and remains stable for long periods. It is also concluded that vein grafts remain patent better than synthetic prostheses or homografts in small vessels.

The author's presentation constitutes a detailed report of the problem as it existed at the time of writing. Developments in this field are so rapid, however, that some of his recommendations concerning arteriography and operative techniques will not be generally accepted. Aortography by injection below the renal arteries is advocated as safer than a higher injection, although other experience has demonstrated that this technique is definitely hazardous because the injection is made into the most diseased portion of the aorta. This monograph should be considered a progress report in the development of the surgery of peripheral arteries. Read in this light it should be of interest to all who deal with this problem.

GEORGE L. JORDAN JR., M.D.

Systema Helminthum. Volume II: The Cestodes of Vertebrates. By Satyu Yamaguti, Professor of Parasitology, Okayama University Medical School, Okayama, Japan. [To be in 3 volumes.] Cloth. Single copy $90; subscription $75. Pp. 860, with illustrations. Interscience Publishers, Inc., 250 Fifth Ave., New York 1; Interscience Publishers, Ltd., 88-90 Chancery Lane, London, W. C. 2, England, 1959.

The first volume of this exhaustive work dealt with digenetic trematodes of vertebrates, and the third volume will discuss the nematodes of vertebrates. The present volume describes tapeworms found in fish, amphibians, reptiles, birds, and mammals. It is designed primarily for laboratory workers in the field of helminthology. Information is presented as briefly as possible, with an accurate description of each tapeworm and the host. If the parasite is found in man, mention is made of that fact, but epidemiology is discussed briefly if at all. The scheme of classification is based on the author's experience in Japan. Hence, new terminology is encountered in some cases, but old names are included for identification. There are drawings, mostly original, of 584 tapeworms. The index is complete, with more than 4,500 names, both old and new. Parasitologists should find this work, financed in part by the Animal Disease and Research Division, United States Agricultural Research Service, a valuable contribution to the literature.

THOMAS HULL, PH.D.

Handbuch der Orthopädie. In vier Bänden. Herausgegeben von Prof. Dr. G. Hohmann, Prof. Dr. M. Hackenbroch, Direktor der Orthopädischen Universitätsklinik Köln, und Prof. Dr. K. Lindemann, Direktor der Orthopädischen Universitätsklinik Heidelberg-Schlierbach. Band III: Spezielle Orthopädie: Obere Extremität. Bearbeitet von B. Andres et al. Cloth. 128 marks; $30.50. Pp. 659, with 424 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart, West Germany; [Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16], 1959.

Twelve authors have contributed one or more chapters to this third volume in a set of reference books. The book is well organized, and the text and the illustrations are presented with clarity and effectiveness. The first chapter describes lesions of the shoulder in newborn infants. Subsequent chapters deal with diseases, injuries, and tumors of the upper extremity. The last chapter describes rehabilitation through occupational therapy. This book is an example of excellent planning and careful editing, and it maintains the high standard set by the preceding two volumes. Every orthopedist should have this book available for reference when faced with difficult or unusual problems affecting the upper extremity.

EDWARD L. COMPERE, M.D.

book with any great degree of understanding. This would force the burden of responsibility of interpretation on the instructor. For instance, in the first 20 pages the author discusses the central nervous system and refers to areas of the brain and their suspected function. These areas are the ones identified and numbered by Brodmann, but Brodmann is not mentioned and it is doubtful that the undergraduate in speech correction would know about the complex system for labeling areas of the cerebral cortex. What emerges is a series of numbers without accompanying illustrations.

There are numerous line drawings. The discussion of the hearing mechanism is too brief and could lead to misconceptions on the part of the student. Various theories of hearing are presented, but none are elaborated on sufficiently to give a complete picture of the complexity of hearing. This textbook tries to give a brief review of the speech mechanism and, in its brevity, leaves much to be desired. It would, therefore, be far too difficult for the average college student, and it contains insufficient detail for the graduate or medical student. As a basic textbook in a course in which there are many outside reading assignments, it should serve a useful function. It is good as an outline on which to base a course in anatomy and physiology as related to speech.

Francis L. Lederer, M.D.

A Textbook of Surgical Physiology. By R. Ainslie Jamieson, M.B., F.R.C.S.Ed., Surgeon, Vale of Leven Hospital, Alexandria, Dumbartonshire, and Andrew W. Kay, M.D., Ch.M., F.R.C.S.Ed., Professor of Surgery, University of Sheffield, Sheffield. Cloth. $11. Pp. 623, with 186 illustrations. Williams & Wilkins Company, 428 E. Preston St., Baltimore 2; E. & S. Livingstone, Ltd., 16 and 17 Teviot Pl., Edinburgh 1, Scotland, 1959.

This valuable contribution to medical literature is dedicated to Professor Illingworth in acknowledgment of his suggestion that the book be written and for his advice and encouragement. The intention was to complement textbooks on surgical anatomy and surgical pathology by providing the surgeon with important, needed information in the field of physiology. This purpose has been accomplished. The text is interesting and well written. It is easy to read and understand. Essential information is generally included, and it is not necessary to search through voluminous detail to get to the point of the subject. If the reader desires background and research information, he may consult the adequate and reasonably up-to-date bibliography.

The material is organized according to anatomic structures or systems. Cross references and a good index make subject matter easily found. As the volume is intended primarily for the general surgeon, discussion of the central nervous system and pituitary has been excluded intentionally, as has discussion of the ovary, which, in Britain, is in the province of the gynecologist. The book does not replace a textbook of physiology, nor was it written for this purpose, but it can be recommended highly to the surgeon, surgical resident, and physician wanting a reference book for physiological facts of importance related to surgical problems.

Oliver H. Beahrs, M.D.

The Human Spine in Health and Disease: Anatomicopathologic Studies. By George Schmorl (†), M.D. Clinicoradiologic aspects by Herbert Junghanns, M.D. First American edition, translated and edited by Stefan P. Wilk, M.D., and Lowell S. Goin, M.D. [Translated from Die gesunde und die kranke Wirbelsäule in Röntgenbild und Klinik, fourth edition, published by Georg Thieme Verlag, Stuttgart, 1957.] Cloth. $21. Pp. 285, with 419 illustrations. Grune & Stratton, Inc., 381 Park Ave. S., New York 16; 15/16 Queen St., Mayfair, London, W. 1, England, 1959.

This monograph presents roentgenograms and photographs of Schmorl's anatomic pathological studies. The clinical and radiologic aspects of the spine in health and disease are presented by Junghanns. In preparing this material and various papers which he has written on the human spine, the author is said to have studied 10,000 spines removed at autopsy. These were examined as gross specimens, by radiographs and in microscopic sections. This is probably the finest and most valuable treatise in the world on the pathology of the human spine. It describes the clinical symptoms and findings which are associated with the pathological conditions described. The extensive bibliography is a valuable contribution.

Edward L. Compere, M.D.

Klinische Röntgendiagnostik chirurgischer Erkrankungen. In zwei Bänden. Von Hans Oberdalhoff, Heinz Vieten und Hermann Karcher. Erster Band. Algemeiner Teil: Röntgendiagnostische Darstellungsmethoden. Spezieller Teil I: Klinische Röntgendiagnostik chirurgischer Erkrankungen der inneren Organe. Von Dr. H. Vieten. Mit einem Beitrag von Dr. H. Dettmar. Cloth. 398 marks for 2 volumes. Pp. 827, with 698 illustrations. Springer-Verlag, Heidelberger Platz 3, (1) Berlin-Wilmersdorf (West-Berlin); Neuenheimer Landstrasse 24, Heidelberg; Göttingen, Germany, 1959.

Three German professors, two of them distinguished surgeons and one a prominent radiologist, have prepared a textbook on roentgenographic diagnosis of surgical diseases. The first volume deals with the discussion of roentgenographic procedures and has an analysis of radiographic findings in surgical diseases of the internal organs. With the exception of the chapter on the urinary system, which was contributed by a urologist, Dr. Dettmar, the first volume is written by the radiologist, Dr. Vieten. His close contact with the surgeons is evident, especially in chapters dealing with normal and pathological postoperative conditions involving the alimentary canal and the biliary tract.

Features distinguishing this book from the many available books on roentgenographic diagnosis are the emphasis that it puts on explaining to the surgeon what information he may expect from the radiologist when confronted with a definite clinical tion of sleep, which varied from one to six hours. Beyond 6 hours, the increase of efficiency was less marked, and 10 hours of sleep had no greater effect than did 8 hours.

SOURCE AND EFFECT OF DIETARY IODINE

To the Editor:—*A 35-year-old woman, treated in the past for what has been termed a "low thyroid condition," has the single symptom of nervousness. The findings of a complete physical examination were normal, but result of a protein-bound iodine test performed in September, 1959, was 22.2 mcg%. The test was repeated at both the same laboratory and different laboratories for confirmation. Results of an exhaustive inquiry concerning possible sources of the iodine intake were negative. She was given potassium iodide and methimazole, 10 mg. four times daily, which had no effect on the protein-bound iodine level in three months. Results of a radioactive iodine uptake test were normal. The result of a protein-bound iodine test performed on her husband was 19 mcg. %. What other tests should be performed? If a source of iodine is discovered, should it be removed?*

M.D., Pennsylvania.

Answer.—Since a high protein-bound iodine level in a euthyroid nongoitrous person usually is due to the ingestion or absorption of excessive iodine, it must be assumed that the inquiry did not reveal the source of an increased iodine uptake. Although all medicaments which may contain iodine have been eliminated, there are drugs which, if given previously, may still be at fault, such as lipiodol used in a salpingogram, bronchogram, or myelogram or even given by mouth. When two euthyroid or hypothyroid members of a family have a high protein-bound iodine level, it may be due to iodine in vitamins, iodine rations, and kelp. To attribute the high protein-bound iodine level in this instance to a high uptake of iodine may not be correct, since the thyroid uptake of radioactive iodine (I^{131}) is normal and would be suppressed if there were an excessive intake of stable iodine. There is at least one drug, iophenoxic acid, which does not suppress the I^{131} uptake but does elevate the protein-bound iodine level for many years. (Astwood, E. B.: Occurrence in Sera of Certain Patients of Large Amounts of a Newly Isolated Iodine Compound, *Tr. A. Am. Physicians* 70:183 [May 7-8] 1957). It is conceivable that there are other iodide compounds with a similar effect. It would be helpful to know the level of inorganic blood iodide. Iodine is present in the serum in two forms, as (1) inorganic iodine and (2) protein-bound iodine. An increased concentration of the inorganic fraction indicates an increase in dietary intake and thus invalidates the chemical protein-bound iodine determination. Determination of the butanol-extractable iodine (B. E. I.) should be carried out, since it is not appreciably altered by the administration of iodides and measures the thyroxine-like compounds contained in the serum more accurately. (Man, E. B., and Bondy, P. K.: Clinical Significance of Serum Butanol-Extractable Iodine, *J. Clin. Endocrinol.* 17:1373 [Nov. 19] 1957.) The basal metabolism test is by no means obsolete and, in this situation, would be an excellent means of assessing thyroid function. Although the physician's clinical judgment is as reliable as any of the laboratory tests in ruling out hyperthyroidism, it is not as reliable in assessing hypothyroidism.

The elevated protein-bound iodine level is likely to cause the curious physician more anguish than it does the patient. Many patients who have had high levels for many years because of previous lipiodol medication show no thyroid disorder. On the other hand, prolonged iodine administration does have a tendency to block thyroid-hormone production and to cause hypothyroidism (Effects of Prolonged Iodine Administration, editorial, *J. A. M. A.* 164:975 [June 29] 1957). The thyroid I^{131} uptake may be increased when the use of the iodine medicament is discontinued. That these patients are receiving excessive iodine could be proved by (1) finding the source, (2) determining the inorganic blood iodine level, and (3) calculating the urinary output of iodine. Although the danger is not great, it would be advisable to eliminate a constant increased intake of iodine (over 5 mg. daily).

POSSIBLE HAZARDS OF TRAMPOLINE

To the Editor:—*The board of the Swiss gymnastic societies intends to introduce "trampolining," i. e., tumbling with use of a trampoline, in its sections. The board inquired whether trampolining poses a hazard to the participants' health or can cause damage to the vertebral spine. Since trampolining is a well-patronized sport in the United States, could you formulate an answer to the board's inquiry?*

H. J. Bluntschli, M.D., Berne, Switzerland.

Answer.—As is true of most other sports, the safety of trampolining depends to a large extent on the supervision given to the activity. It requires very careful "spotting" or guarding by other gymnasts while one person is performing. Such spotting is, of course, routine in connection with the use of most gymnastic apparatus.

Another factor pertaining to safety in the use of the trampoline is that it should never be left set up in the gymnasium or play area to be used indiscriminately by amateurs without proper instruction and supervision. To introduce the trampoline and to teach gymnasts its use will require provision of a corps of qualified instructors to train and instruct others who may wish to purchase and use this equipment.

Serious accidents have occurred on the trampoline, and some of the injuries sustained were to the neck and the back. It is reported that a few have oc-

QUESTIONS AND ANSWERS

ANTICOAGULANT THERAPY AND OPERATIONS

To the Editor:—*What is the management of a patient who is receiving long-term anticoagulant treatment and must undergo an operation?*

M.D., New York.

Answer.—Patients on long-term anticoagulant therapy are usually receiving a hypoprothrombinemic agent, either a coumarin or a phenindione derivative. These compounds vary widely, not only in their ability to depress prothrombin levels more or less quickly but, when administration of the drug is discontinued, in the rate of return of prothrombin to normal values, which varies considerably. On simple withdrawal of the drug, it may take five days for a patient to be free from the effects of bishydroxycoumarin and three days for ethyl biscoumacetate. Furthermore, in different patients receiving any one of these drugs there is considerable variation in prothrombin response to withdrawal of the drug.

When use of anticoagulants is indicated prior to an elective surgical procedure, it is best to maintain the patient on heparin sodium therapy alone for one week prior to the day before the operation, and it must be established that prothrombin and clotting times are normal.

If a patient taking a hypoprothrombinemic agent requires an emergency surgical procedure, administration of phytonadione (vitamin K_1) is required. Slow intravenous injection of 50 to 150 mg. of vitamin K_1 is usually satisfactory, though some hours may be required to achieve the desired result. If the prothrombin level is still depressed, a second injection may be necessary. Postoperatively the prothrombin level may again fall for several days because of the delayed action of the hypoprothrombinemic agent, and an additional dose of vitamin K_1 may be necessary. If it is important, postoperatively, to restore an anticoagulant effect promptly, heparin should be used.

If a patient on full heparin sodium therapy requires an emergency surgical procedure, 50 to 100 mg. of protamine sulfate in 1% solution is said to neutralize the circulating heparin sodium rapidly.

Transfusions of fresh whole blood often control unexplained bleeding in patients who have received anticoagulants but are not ordinarily administered until the procedures listed above have been carried out.

HISTAMINE INJECTIONS DURING PREGNANCY

To the Editor:—*Are injections of histamine, given two to three times weekly, contraindicated in pregnancy? The injections are being administered to a 30-year-old woman for control of Ménière's syndrome.*

James B. Gault, M.D., Creston, Iowa.

Answer.—The older obstetric literature contains many reports on the oxytocic effects of histamine. These, however, were based on in vitro studies or after the administration of large doses. It was assumed that the increase in the plasma histaminase level would render pregnant women more tolerant to histamine, but this is apparently not so. Pregnant and nonpregnant women have similar responses to the same threshold dose (Kahlson, in "Histamine," Ciba Foundation Symposium Jointly with Physiological Society and British Pharmacological Society on Histamine, Boston, Little, Brown & Company, 1956).

Therapeutic doses of histamine were given to 15 women throughout pregnancy at the Mayo Clinic without deleterious effect (McElin and Horton, *Am. J. M. Sc.* 218:432 [Oct.] 1949). No oxytocic effects were observed. The largest dose given was 1 mg. intravenously (calculated as histamine base). The minimal amounts that produced symptoms ranged from 4 to 30 mcg. (of base) given intravenously. The effective doses are the same in pregnant and nonpregnant women (Janowitz and Grossman, *Am. J. Physiol.* 157:94 [April] 1949).

EFFECTS OF LACK OF SLEEP

To the Editor:—*The studies on sleep deprivation by Brauchi and West, appearing in* The Journal, *Sept. 5, 1959, page 11, are limited to the effects of sudden deprivations of absolute nature. Has any work been done to determine the effects of various degrees of sleep deprivation that is continued for prolonged periods? Such studies may reveal a truer aspect of sleep deprivation as related to human biological activities.*

M.D., Pakistan.

Answer.—There are no studies on the effects of continued curtailment of sleep for prolonged periods. A study by Viaud (*C. R. Soc. Biol.* 139:553 [June] 1945) determined the efficiency of performance in three mental and neuromuscular tasks after varying amounts of sleep. Tested at the peak of daily efficiency (3 p. m. to 5 p. m.), the restorative effect of the previous night's sleep was found to increase in almost linear fashion with the dura-

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curred even when adequate spotting and supervision had been provided. A certain degree of hazard is connected with the use of any athletic apparatus and cannot be entirely eliminated without stifling the sense of adventure derived from the activity.

It is difficult to determine whether trampolining offers a greater hazard than other sports. The New York High School Athletic Association, which offers to students an insurance policy against injuries sustained in physical education and athletic activities, has reported as follows: Among the 114,457 insured by the Association (1953-1954), 12 students (7 boys and 5 girls) were injured on the trampoline. Of these injuries, eight were sprains, three were contusions, and one was dental. Five of the injuries occurred to the back, three to the ankle, two to the neck, and one to the teeth. The average insurance claim for trampoline injuries amounted to $13.25, compared to an average of $14.03 for all other physical education and intramural injuries.

Additional information on the safety of trampolining might be obtained from the American Association for Health, Physical Education, and Recreation, 1201 16th St. N. W., Washington 6, D. C., and the National Recreation Association, 8 W. Eighth St., New York 11.

WHAT CONSTITUTES A QUORUM?

To the Editor:—*Is it customary for a hospital to have in its bylaws a statement or regulation which defines what constitutes a quorum for meetings of the medical board and its subcommittees?* *M.D., New York.*

Answer.—"The number which constitutes a quorum of an organization or committee is usually stated in its constitution or bylaws. In the absence of a provision which determines the quorum, common parliamentary law fixes the quorum at a majority of the members of the organization. It is legal and common practice for organizations to fix their quorum at less than a majority of the members. A committee requires a majority of its members for a quorum unless special provision is made for a different number. Since a majority of the quorum, which is often a very small proportion of the total membership, has the right and power to make decisions for the organization, rigid requirements for notices of meetings should be made in order that all members will have an opportunity to be present." This is a direct quotation from Sturgis' "Standard Code of Parliamentary Procedure."

TETANUS TREATMENT AND PROPHYLAXIS

To the Editor:—*In Questions and Answers in* The Journal, *Dec. 12, 1959, page 2156, the answer states, "should a patient be highly sensitive to tetanus or diphtheria antitoxin, the usual method of desensitization (repeated administration of small doses at frequent intervals) may be too time-consuming. Intravenous administration of heparin, 20 mg. per kilogram of body weight, will prevent serum reaction and anaphylaxis. It may take up to 18 days for complete elimination of foreign protein (antitoxin) from the blood stream; therefore it is necessary to keep the patient heparinized during that time."*

If heparin is effective for this purpose, this fact should be made common knowledge. It appears that this information is lacking in the standard textbooks on pediatrics and communicable diseases. I consulted several authorities who expressed doubt and incredulity.

Jawetz and co-authors (Review of Medical Microbiology, Lange Medical Publications, Los Altos, Calif. 1958), state that anaphylaxis results in the liberation of heparin and diminished coagulability of the blood. Boyd (ibid., p. 799) states that in anaphylaxis in the guinea pig the coagulation time of blood is prolonged and that in man there is decreased blood coagulability.

I believe that desensitization of a highly sensitive patient to a degree which makes safe the intravenous use of therapeutic doses of horse serum is a situation in which infinite caution is combined with incredible luck.

A greater dissemination of the information concerning the usefulness of heparin in human beings and its reliability under clinical conditions seems to be indicated.

Edward B. Shaw, M.D.
University of California
San Francisco Medical Center
San Francisco.

The above comment was referred to the consultant who answered the original question, and his reply follows.—Ed.

To the Editor:—*It is unfortunate that the results of many good scientific experiments, which have been and are being published in nonmedical journals of allied scientific fields, are not applied to useful purpose in medicine more often. Like sulfanilamide and many others, the use of heparin is a case in point.*

In anaphylactic shock, fibrinogen is rapidly precipitated in the vascular beds as fibrin: i. e., prevent fibrin precipitation, prevent anaphylactic shock. I have seen Professor Kyes demonstrate this repeatedly in sensitized animals. He also used it successfully against 1 M.L.D. of Crotalus venom in animals, in either instance the control untreated animals dying and the heparinized animals surviving.

I agree with Dr. Boyd's viewpoint about desensitization, especially if time is a factor.

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